MALIGNANT DISEASE OF THE URINARY TRACT *

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1773, the year of the foundation of the Medical Society of London by Lettsom and of the Boston Tea-party, also saw the birth in Frankfurt of a certain Bozzini. He was the inventor of the first cystoscope, a primitive instrument in which light from a candle was reflected down a long tube passed into the bladder. Two years after the delivery of the first Lettsomian lecture Desormeaux added a lens and a gas lamp; and in 1876 Nitze produced the prototype of the modern cystoscope. The discovery of X rays by Röntgen in 1895 was another milestone in urological diagnosis; and it was in the same year that Rehn reported an increased incidence of bladder tumours among aniline dye workers.

THE BLADDER

I have reviewed the notes of 565 of my patients with carcinoma of the bladder. No cases have been included unless malignancy was verified either histologically at the time or by subsequent events. The sex-incidence was 417 males to 148 females. Their ages ranged from twenty-three to ninety, with an average of sixty-two years.

Pathology

Types

Carcinoma of the bladder is seen in two main forms which differ so much in appearance and behaviour as to suggest two different diseases.

On the one hand there is the *papillary tumour*: it resembles the benign papilloma, save that its villi tend to be more stunted, its pedicle is wider, and its surface is often flecked with phosphates. These tumours may be single, but they are often multiple or confluent; they should be regarded as a disease affecting the mucosa of the whole bladder. They can spread in a wound by spill and implantation when the bladder is opened, and such implants often lose their gross papillary form and become solid. In the course of time they can infiltrate the muscle layer and penetrate the perivesical tissues. Lymphatic or vascular metastases may also be found; but spread is mainly along the mucous or submucous lining and by bulky proliferation into the cavity of the bladder itself.

On the other hand there is the *solid tumour*, nodular in cystoscopic appearance, usually single and localised. Its tendency is to infiltrate the underlying muscle early, to invade lymphatics and blood-vessels, and in time to become fixed to the pelvic wall. It has a higher intrinsic malignancy than the papillary tumour and it must be caught early if it is to be cured.

Stage

The extent of penetration into or through the bladder wall determines the stage of the disease; it is important in assessing operability and prognosis. It can only be told with certainty after the whole thickness of the wall, or the whole bladder, has been removed; but a fairly accurate clinical assessment can be made on bimanual examination under full anæsthetic relaxation. I have grouped all my cases in which staging was possible into groups A, B, and C. corresponding with the mucosal, muscular, and perivesical stages of infiltration.

Grade

Another pathological feature which influences the behaviour of bladder cancer is the histological degree of malignancy, known as the grade of the tumour. For many years we have followed the system, described by Dukes and Masina (1949) of recognising three such grades—low, medium, and high. Though there is a correlation between grade and stage, the grade of malignancy is more important in the papillary tumours, whilst the stage of penetration gives most information in the solid growths.

Rare Forms

Pure squamous-cell growths occur, apart from tumours which show areas of squamous metaplasia: and primary columnar-cell adenocarcinomas may arise from the urachus or from the mucous glands of the base. There are 3 cases of sarcoma in this series.

Diagnosis

Hæmaturia is the outstanding clinical feature of cancer of the bladder: in this series it was present in 97% of over 500 patients. In secondary growths, due to extension from other viscera, the proportion of patients with hæmaturia was 75%. Occasionally the first symptoms are those of cystitis with frequency and pain, but the urine is often sterile.

Cystoscopy with a small examination cystoscope under a local anæsthetic usually suffices to establish the diagnosis; but the investigation should always be repeated under a general anæsthetic with an instrument with a good irrigating channel, a clear wide-field telescope, and plenty of time.

The excretion pyelogram will show whether the upper urinary tract is normal; a dilated ureter above a growth usually indicates infiltration. A "bite" deformity in the cystogram is suggestive of a solid growth, whilst a papillary tumour can be recognised by the irregular distribution of the medium between the fronds. The size of the tumour can be assessed with reasonable accuracy from the X-ray pictures.

At the time of cystoscopy a piece of the growth should be removed for biopsy; and the empty bladder should always be examined bimanually under full relaxation. A tumour of average size is palpable; a solid tumour is firm and may be mobile or fixed; a papillary tumour is softer and more often mobile within the bladder. A firm easily palpable tumour indicates infiltration of the bladder wall. The urine should be examined bacteriologically.

Treatment

Guiding Principles

New types of treatment continue to appear: and the clinician must be constantly ready to change his method of attack. I believe that the greatest hope at present lies in the combination of surgery and radiotherapy. The collaboration between the two must be a true partnership for the benefit of the patient, and in no sense must it be competitive. Perhaps when our concepts of ætiology are further clarified our treatment will become partly biochemical.

* Based on the first of three Lettsomian lectures for 1958 delivered before the Medical Society of London. The full text will later appear in the *Transactions* of the society.

If the disease is one which affects the whole bladder, then treatment should in theory be by total cystectomy or total irradiation. As it is the papillary growth which has this tendency most, one might make a case for total cystectomy or irradiation for all papillary tumours. Yet experience shows that if such tumours are not extensive when first seen they can be kept in control by local treatment, and some do not recur. 70% five-year survival can be obtained by cystodiathermy alone in papillary carcinoma of low malignancy; but the high recurrence-rate shows the widespread liability to the disease.

Solid growths, on the other hand, more often appear as single lesions. If seen early and in an accessible position they can be removed by partial cystectomy or segmental resection with good prospect of success. Too often, however, they have reached the stage of perivesical or distant spread, or they are of high malignancy. In such cases control is unlikely, whatever the method of treatment, though considerable palliation can be given by supervoltage X-ray therapy.

Radiosensitivity is directly proportional to the degree of malignancy, and the finding of a high degree in a papillary tumour should be an indication to introduce some form of irradiation into the treatment. Whilst conventional (200 kV) therapy has a limited value, the possibilities of the supervoltage machines are much greater (Busby 1957, Swinney 1957, Cavazzana 1957). I am fortunate in having the collaboration of Professor Windeyer with the large machines at Mount Vernon Hospital. Our two-year experience with them is too recent for the presentation of results in detail, but we can report a satisfactory regression in papillary tumours and better palliation in the infiltrating growths than by any other method.

Though supervoltage therapy has the great advantage of producing little general reaction and only slight skin changes, one untoward result of any form of effective irradiation is the production of telangiectases in the bladder. These small vessels have a tendency to bleed, arousing a suspicion of recurrence. Light cystodiathermy may check the bleeding; but too deep coagulation may make it worse. Another occasional unpleasant sequel is radionecrosis and a contracted bladder; it is more common if the treatment has been given too quickly. I have seen it in 2 cases treated by intracavitary irradiation with a solid bead of cobalt-60, both of which needed cystectomy, and in 2 whose growths were very effectively treated by Mr. Wallace with intracavitary liquid isotopes.

Diversion of Urine

Urinary diversion is necessary before total cystectomy and must be seriously considered before radical X-ray treatment. Ureterocolostomy has fallen somewhat out of favour owing to the risk of acidosis; but ureteroileostomy, which is free from this risk, carries the need to wear a receptacle for the urine. Though most patients manage the receptacle well, I feel that there is still a place for ureterosigmoidostomy with proper electrolyte control.

I have also done palliative urinary diversion in 50 cases, and palliative cystectomy, where the growth was already beyond the bladder, in another 34. 9 further patients were deemed untreatable by surgery or by irradiation when first seen. Of these 93 patients, for whom there was no real hope of cure, 16 lived for more than a year; 1 lived and worked for seven years after cystectomy, before dying from metastases; and 1 remarkable man is still alive and working more than eight years after ureterocolostomy followed by excision of the dome of the bladder and the insertion of radium needles into an anaplastic carcinoma that was adherent to the pubes. Palliative surgery in this disease will not give good statistics but it will often prolong life in comfort.

Choice of Treatment

For the potentially controllable case there is a wide choice of treatment, but we must realise that tables of results compare not so much the merits of different methods as the different types of growth encountered. Good results are an indication that the right type of treatment was chosen for that particular growth: bad results show that either the wrong treatment was chosen, or that the tumour had a very high intrinsic malignancy, or that it was too far advanced when first seen. The choice depends on the general condition and renal function as well as on the type, size, situation, multiplicity, and extent of the tumour, and on the presence of mucosal changes beyond it.

PAPILLARY TUMOURS

Cystodiathermy

For localised, pedunculated, papillary, differentiated growths of small or moderate size my preference is for coagulation diathermy with removal of any residual stump by the resectoscope or biopsy forceps.

The usual small bladder electrode is insufficient, except for small tumours; and I have found that a modification of Kidd's cystoscope increases the range of the operation enormously. The instrument ends in a big ball electrode: it has a wide field of vision, and, of greatest importance, the same large irrigation fitting as the standard cystoscope. Tumours of considerable size can be destroyed at one sitting; and it is the first treatment which matters most. Repeated nibbles at the surface with a small electrode are unsatisfactory and may be harmful.

Endoscopic treatment was used in 153 cases; and the five-year survival-rate is shown in table I.

TABLE I—FIVE-YEAR SURVIVAL-RATE AFTER TREATMENT BY CYSTODIATHERMY

—	No.	5-year survival
Low grade or stage	112 (73%)	43/60 (72%)
High grade or stage	41 (27%)	8/25 (32%)
Total	153	51/85 (60%)

Operative mortality, 1/153 (0·6%). 10-year survival, 13/40 (33%).

Survival for any given period does not tell the whole story, for 75% of these patients needed more than one session of treatment. The so-called recurrence-rate often represents residual tumours: it appears to be lessening since the adoption of the big-ball cystoscope during the past two years. Distant metastasis is uncommon from a low-grade tumour, but it can occur at any time.

Open Diathermy Excision

In patients with papillary tumours too large for cystodiathermy, or who are unfit for total cystectomy, the bladder can be opened and the growths excised down to the muscle. The method was also used for a time, wrongly as we now think, for inoperable high-grade or infiltrating tumours: in them it affords poor palliation. In any case spill of urine or tumour is a danger that must be avoided. In the low-grade but extensive cases the survival is remarkably good so long as regular follow-up cystoscopies and diathermy treatment are carried out.

Of the 28 patients treated in this way 3 subsequently needed total cystectomy, 1 of whom is alive ten years later. There have been 7 five-year survivors and 3 ten-year survivors. There was 1 operative death.

Excision of Mucosa

As a variant of open diathermy excision I have on 2 occasions excised the mucosa of the bladder.

A woman of fifty-eight had extensive papillomatosis. I removed the whole area down to muscle with the diathermy needle but left a little apparently normal mucosa on the trigone and around the ureteric orifices. In over two years she has had two small recurrences, but the mucosa has regenerated completely. Histologically the tumours were papillomata.

The other patient, a man of sixty-one, had cystodiathermy in 1952 and 1953 for a low-grade non-infiltrating papillary carcinoma with some squamous metaplasia. He defaulted until 1957 when he returned with a bladder full of papillary growth. In October, 1957, I excised the entire mucous membrane of the bladder. A month later the bladder had a more normal appearance on excretion urography, but he had hourly frequency. A cystogram at two months, whilst showing a smooth bladder outline, also showed a bilateral ureteric reflux. Three months after operation cystoscopy showed for the most part a pale trabeculated bladder with no apparent mucosa. There were some red areas where mucosa appeared to have regenerated; and biopsy confirmed this. There was no recurrence of growth but the capacity was only 3 oz. The bladder was distended by a balloon to $7^1/_2$ oz. This caused considerable bleeding which lasted for twenty-four hours but resulted in some improvement of his frequency. It is still possible that he will have to undergo urinary diversion.

TABLE II—FIVE-YEAR SURVIVAL-RATE AFTER TREATMENT WITH RADON SEEDS

Grade	No.	5-year survival
Papillary differentiated	49	26/37 (*70%*)
Poorly differentiated	33	12/24 (*50%*)
Anaplastic	18	5/12 (*42%*)
Total	100	43/73 (*59%*)

Operative mortality 4/100 (*4%*).

I cannot recommend this operation yet: but recent American work on dogs had shown that, after mucosal denudation, bladder contracture and ureteric reflux do not occur if a cuff of mucosa is left around the ureteric orifices (Sanders et al. 1958). My 2 cases confirm this observation.

Intravesical Implantation of Radioactive Material

When a papillary tumour is of high-grade malignancy, its chances of recurrence after cystodiathermy are high; and a better result can be expected from an implant. I have used radon seeds since 1946; but in 1956 I changed to gold grains irradiated in the atomic pile. The effect of the two appears to be the same. Irradiated tantalum wire can also be used: and, since it has a half-life of 112 days, some can be kept in stock. I believe, however, that it is more often followed by radionecrosis than the other two substances. Insertion is preferably done by open operation: the implant is permanent and the bladder can be closed. I have used radon seeds in exactly 100 cases (table II).

The local result of radon implantation in an anaplastic growth may be excellent; but it may not prevent distant metastases in the liver and aortic glands.

On comparing five-year survivals there is nothing to choose between cystodiathermy and radon implantation in respect of low-grade tumours. In high-grade tumours radon shows an appreciable gain. Treatment for recurrences was necessary in 75% of the diathermy cases and only in 42% of the implants.

Cystectomy

Although partial cystectomy is sometimes suitable for large papillary tumours, there are often mucosal changes, or even small tumours, remote from the main growth; and these make total ablation the better procedure. For extensive or multiple papillary tumours total cystectomy offers the best prospect of complete control. It carries the added risk of deviation of the urine; and it should not be left to be undertaken as a last resort, as so often happens. The operation has its best results in tumours of low malignancy (table III). The newer forms of radiotherapy have got to prove themselves before it can be abandoned.

TABLE III—FIVE-YEAR SURVIVAL-RATE AFTER TOTAL CYSTECTOMY

Group	No.	5-year survival
A (mucosal)	37	11/28 (*39%*)
B (muscular)	39	3/31 (*10%*)
C (perivesical)	34	1/24 (*4%*)
Total	110	15/83 (*18%*)

Operative mortality, 14/110 (*12·7%*)

The statistical results of total cystectomy appear poor, but the operation is generally used for the most extensive cases of papillary tumour. Of the 11 patients in group A who passed the five-year mark 10 are still living and 1 died from heart-disease after eleven years. Muscular penetration worsens the prognosis considerably; and when there is perivesical extension the operation should be regarded as palliative.

SOLID TUMOURS

Localised solid nodular tumours, the "bun" carcinomas—if they are not too large, if they do not involve the bladder base, and if there are no mucosal changes elsewhere—are best treated either by partial cystectomy or by extravesical radium implantations.

Partial Cystectomy

The excision must be generous and include the whole thickness of the bladder with a patch of peritoneum.

TABLE IV—FIVE-YEAR SURVIVAL-RATE AFTER PARTIAL CYSTECTOMY

Group	No.	Survival	
		10 years	5 years
A (mucosal)	17	3/9 (*33%*)	7/12 (*58%*)
B (muscular)	56	9/32 (*28%*)	16/44 (*36%*)
C (perivesical)	15	0/6 (*0*)	0/6 (*0*)
Total	88	12/47 (*26%*)	23/62 (*37%*)

1 sarcoma survived $6^1/_2$ years. Operative mortality 6/89 (*6·7%*).

Mucosal changes beyond the tumour determine the need for total cystectomy. In my experience this type of bald tumour is getting less common than the mixed solid and papillary type of high-grade malignancy with infiltration (table IV).

Chances of survival at ten years and at five years diminished with increasing depth of penetration of the bladder wall: only 2 patients with perivesical extension lived for more than one year. Those with muscle penetration predominated; and survival of 28% at ten years was surprisingly good. The most favourable site is the dome. There were 4 cases of urachal tumour in which the umbilicus and urachus were excised en bloc with the bladder tumour. 1 is still living over twelve years later. For tumours near the ureteric orifice there should be no hesitation in reimplanting the ureter. This was done in 14 patients and only 2 kidneys were lost. The longest survivor, now eighty years old, was operated upon more than twenty-one years ago and had the ureter reimplanted. At no period, however, can one speak of "cure". New tumours, the so-called recurrences, may come at any time. Mostly they are of the same grade as the original, but a different tumour may appear.

Radium Implantation

Because of the severe and prolonged cystitis which affects the bladder if it cannot be immediately closed, the implantation of radium needles from the inside is out of favour. Higham (1955), however, has devised an ingenious method of application on a rubber mould which does allow closure. In accessible solid tumours it is possible to implant radium from outside without opening the bladder. When high-grade malignancy indicates the need for irradiation this is an alternative to partial cystectomy. I have treated 15 patients in this way, all but one with high-grade solid tumours. The longest survivor is still living after nearly five years. Even if not curative the local irradiation may make the tumour operable.

Intracavitary Irradiation

Much—perhaps too much—was hoped from a method which promised uniform irradiation of the whole bladder from a central source. The results of treatment are shown in table v. Cobalt 60 was used in 11 cases and radium in 2.

TABLE V—RESULTS OF TREATMENT WITH INTRACAVITARY IRRADIATION

Lived 3–5 years	4
Lived 1–2 years	6
Lived less than 1 year	2
Operative mortality	1

The only real successes were in non-infiltrating papillary tumours; and the method has now been abandoned.

MISCELLANEOUS TUMOURS

In the series there were 11 cases of growth in a diverticulum. Most of these are of high grade and infiltrate quickly through the thin wall of the sac, becoming fixed. In 32 cases the bladder was invaded from some other viscus: in 13 the primary growth was in the uterus or ovary, in 4 in the large intestine, and in 15 in the renal pelvis or urethra. Sometimes wide excision of two invaded viscera is possible; and occasionally a pelvic clearance is indicated. The cure of a vesicovaginal fistula is always worth while.

3 cases of sarcoma were treated by combined irradiation and surgery; 1 lived for eight years; 1 for six and a half; and 1 is living at nearly four years.

Conclusions

I have tried to indicate that cancer of the bladder exists in two principal forms. The papillary differentiated growth can be relatively benign and readily controlled: the solid anaplastic tumour is always very malignant.

Duplicity in the more worldly sense is evident from the insidious clinical onset and the late recurrences of the disease. The prognosis may appear to depend more on the type of growth than on the treatment, but the disease does at least run true to form. It will give early warning of its potential malignancy if the patient is fully examined and carefully assessed.

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THE MEASUREMENT OF THE PREVALENCE OF ISCHÆMIC HEART-DISEASE

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EVIDENCE from death-rates, autopsy studies, and hospital and clinicians' records suggests that the amount of ischæmic heart-disease differs in different communities (Keys and White 1956). Such evidence has been invaluable in suggesting hypotheses about the ætiology of the disease which require testing quantitatively in more representative samples of the population.

Of the two epidemiological indices of morbidity, one would prefer to know the attack-rate (inception-rate or incidence) or rate of appearance of ischæmic heart-disease in the community. This, however, is difficult to measure, because it needs a detailed follow-up of a large, fully examined, and well-defined group. The alternative index, prevalence (i.e., the proportion with ischæmic heart-disease in the community at a given time), is an essential preliminary measurement for establishing attack-rates, is more readily determined, and is the one considered in this paper.

In the United States the measurement of both these indices is in progress, and preliminary results have been published (Dawber et al. 1957, Doyle et al. 1957, Chapman et al. 1957, Epstein et al. 1957, Drake et al. 1957). These admirable studies are open to possible criticism, however, on the ground that, although attention is always paid to diagnostic criteria, reproducibility of these criteria has not been investigated, and consequently it is impossible for others, obtaining different values for the prevalence of ischæmic heart-disease in other populations, to know whether they are dealing with an artefact or a true epidemiological difference.

Both Doyle et al. (1957) and Chapman et al. (1957) studied groups of Civil Service employees, the former in New York State, the latter in Los Angeles, while Epstein et al. (1957) investigated New York clothing workers. Such working populations are not necessarily representative of the whole community from which they were drawn, since, apart from occupational self-selection and social class, those who may have retired because of ill health are automatically excluded. Lastly, bias could have been introduced by the rather high refusal-rates in Framingham (31%) (Dawber et al. 1957), and Los Angeles (25%) (Chapman et al. 1957).

Hence there seems to be a real need for techniques for measuring ischæmic heart-disease in unselected populations and ensuring comparability of the medical indices used. We discuss these two problems, using material from a survey of representative occupational samples of two communities.

Prevalence is essentially a ratio—in the present context the ratio of those suffering from ischæmic heart-disease to the population at risk. Difficulties and errors may arise, therefore, not only in identifying the cases of ischæmic heart-disease but also in defining, sampling, and measuring the community from which they are drawn. The latter problem is usually neglected—partly because its impor-

tance is not appreciated, but partly perhaps because people are secretly rather frightened of it.

Measurement of the Population at Risk

Our method has been to define a geographical area, enumerate the inhabitants by a private census, and then carry out a chest X-ray survey (Cochrane et al. 1955, Cochrane, Miall, and Clarke 1956). The information thus obtained is transferred to punch cards from which samples can readily be drawn.

The first of the two surveys of ischæmic heart-disease was made in 1954 on a random sample of miners and ex-miners living in the Rhondda Fach, a mining valley in South Wales (Thomas et al. 1956). The second survey was designed to achieve an occupational contrast. An agricultural area, the Vale of Glamorgan, which is 15 miles from the Rhondda Fach, was chosen, and in 1956 a random sample of men aged 55–64 who lived in this area and had never been miners was investigated.

Those who appeared in the sample were visited by members of the epidemiological team at the Pneumoconiosis Research Unit and persuaded to cooperate. The vast majority were transported either to the unit or to a centre in Cowbridge, in the Vale of Glamorgan, where the examination took place. The " response " rate and other details are shown in table I.

The first survey was a pilot investigation in which the sample was limited to 55 men. In retrospect we consider this too few, and in the second survey we increased the sample to 100. Certain problems are introduced by the measurements being made some time after the nominal census. The sample will inevitably include some people who have died or left the area in the interval. We have not attempted to substitute others for these, but we have carefully investigated the cause of death in the former and have excluded the latter from the population at risk.

TABLE I—RESPONSE-RATE IN THE TWO SURVEYS

Area	No. in sample	No. left area	No. dead	No. of refusals	Response-rate of those still in area and still alive
Rhondda Fach ..	55	2	2	4	47 (92%)
Vale of Glamorgan	100	4	1	10	85 (90%)

The other source of error relates to the proportion of the sample responding to our persuasion. The percentages shown in table I are high. They could, of course, be higher, but at present we know of no technique for reducing the refusal-rate below 5–10%. Possibly others will discover one.

Measurement of the Number with Ischæmic Heart-disease

The diagnosis of ischæmic heart-disease is usually based on clinical, radiological, and electrocardiographic evidence. Analysis of the results of the first survey suggested strongly that the electrocardiogram was by far the most important factor in making the diagnosis, that the clinical examination was sometimes valuable, and that the posteroanterior chest X-ray was relatively unimportant. Further investigation shows that there is considerable variation in the diagnosis. Comparison of the conclusions of several cardiologists, based on clinical and electrocardiographic examination of all members of the sample, would have been desirable; but this proved impossible and we have had to compromise. In both surveys we have arranged for the same clinician to make a diagnosis on the clinical and electrocardiographic evidence. In addition, all the electrocardiograms have been interpreted by two other cardiologists.

Our two main problems have been (1) the difficulties of obtaining satisfactory electrocardiograms and (2) the difficulties associated with different interpretations of the same tracing.

Technically perfect electrocardiograms are harder to obtain under survey conditions than in hospital—partly because time is limited and partly because it is difficult or impossible to recall a member of the sample in order to repeat the investigation. In neither of our surveys were the electrocardiograms perfect: but in the second survey they were much better than in the first, and in a more recent survey they were nearly up to the best hospital standard. There is, in addition, the question of which leads and how many should be taken to satisfy different cardiologists. In future we intend to take the 12 standard limb and chest leads. Our experience also suggests that a direct-writing electrocardiograph has considerable advantages over one recording photographically. Unsatisfactory tracings can be immediately repeated before the subject departs, and additional leads can be added at the discretion of the cardiologist making the clinical examination.

The differences of interpretation presented a more serious problem. Photographic prints of the electrocardiograms from the two surveys (concealing the origin of the tracings) were mixed at random and read independently by each of the three cardiologists, who were asked to record their observations on a standard form. The cardiologists* reported on the tracings as they would have done in ordinary clinical practice. They held no prior discussion on the criteria for diagnosing ischæmic heart-disease. The diagnostic criteria used by the third observer (A. J. T.) were those detailed previously (Thomas et al. 1956) and we expected that those used by the other two readers would be broadly similar. The results are shown in table II. It is clear that there were considerable differences of interpretation. The commonest cause of disagreement was the borderline tracing; next was the difficulty of differentiating cardiac hypertrophy, with or without associated strain, from ischæmia; and lastly, some differences may have been due to unsatisfactory tracings and to the wording of the form (but exclusion of the unsatisfactory electrocardiograms did not produce any significant improvement). In future surveys we shall use a more precise form. Observer differences might be further reduced by preliminary discussion of precisely what abnormalities are to be accepted for diagnosis.

In view of the observer differences we have adopted two indices for the analysis of the results. When the diagnosis of ischæmic heart-disease has been reached on complete clinical, radiological, and electrocardiographic assessment, we speak of the " clinical " index; when we have used those electrocardiograms which all three observers regarded as showing ischæmic heart-disease we speak of the " electrocardiographic " index. The advantage of the first index is the use made of the valuable information supplied by the clinical examination. Its main disadvantage is the difficulty, in comparative studies, of preventing possible bias through the clinician knowing the area from which the subject comes. The advantage of the " electrocardiographic " index is the ease with which such bias can be avoided.

Results

Prevalence in the Two Areas

If we restrict ourselves to the two indices we can compare the prevalence of ischæmic heart-disease in the two

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TABLE II—PREVALENCE OF ISCHÆMIC HEART-DISEASE DIAGNOSED CLINICALLY AND/OR ELECTROCARDIOGRAPHICALLY IN THE TWO COMMUNITIES BY VARIOUS READERS

—	Vale of Glamorgan (85 cases)	Rhondda Fach (47 cases)
Diagnosed clinically (clinical index) ..	19 (22%)	18 (38%)
Diagnosed electrocardiographically:		
By all 3 readers (electrocardiographic index)	12 (14%)	10 (21%)
By 2 of the 3 readers	6 (7%)	2 (4%)
By 1 of the 3 readers	16 (19%)	10 (21%)
Total (by any of the 3 readers)	34 (40%)	22 (47%)
Corrected * clinical index	22 (25%)	18 (38%)
Corrected * electrocardiographic index ..	15 (17%)	10 (21%)

* When the 3 additional Vale cases are included.

populations, as shown in table II. This, however, is not entirely satisfactory.

Among those who refused examination there were 2 in the Vale of Glamorgan who had been diagnosed in hospital as suffering from ischæmic heart-disease and whose electrocardiograms were reviewed by one of us (A. J. T.). It was impossible to include their electrocardiograms in the series sent to the three readers, but we think that they should be added to both indices. The case of the man who appeared in the sample but died of ischæmic heart-disease before the survey presents a somewhat different problem, but we believe that he too should be included in both indices. The effect of these additions is shown in table II. The difference between the two areas is much reduced.

We conclude that we have not been able to prove the existence of a significant difference in prevalence of ischæmic heart-disease between the two areas. The possibility of its existence has not, of course, been excluded.

Characteristics of Populations in Relation to the Disease

Another advantage of this type of prevalence study is the opportunity it gives of comparing those with ischæmic heart-disease with those of the same age and sex living in the same area without ischæmic heart-disease. Such a control group is clearly preferable to the more usual one, drawn from hospital patients.

Personal and anthropometric characteristics (table III).—There was little difference in either area in the average age of the ischæmic and control groups. Both indices showed a considerable difference in average weight between the two groups, and smaller differences in standing and sitting height; and in nearly all cases the " electrocardiographic "

TABLE III—ANTHROPOMETRIC CHARACTERISTICS

—		Vale of Glamorgan		Rhondda Fach	
		Ischæmic heart-disease	Others	Ischæmic heart-disease	Others
No. in group	E.C.G.	12	73	10	37
	Clinical	19	66	18	29
Age (years)	E.C.G.	58·6	59·5	61·0	60·6
	Clinical	59·7	59·3	61·1	60·6
Standing height (inches)	E.C.G.	66·9[1]	65·6	66·7	66·2
	Clinical	66·0	65·7	66·6	66·0
Sitting height (inches)	E.C.G.	35·3[2]	34·6	34·7	34·4
	Clinical	34·8	34·7	34·7	34·4
Weight (pounds)	E.C.G.	166·3[3]	150·2	156·8	138·8
	Clinical	160·2	149·9	156·9[4]	133·8
Arm girth (inches) ..	E.C.G.	10·7	10·4	..	..
	Clinical	10·6	10·4	..	..
Arm skin fold (cm.)	E.C.G.	8·8	9·3	..	..
	Clinical	9·5	9·2	..	..

1. $0{\cdot}015>P>0{\cdot}01$. 2. $P<0{\cdot}001$. 3. $0{\cdot}015>P>0{\cdot}01$. 4. $0{\cdot}005>P>0{\cdot}001$.

index, which probably indicates the more severe cases, gives a greater difference than the " clinical " index. Arm girth and arm skinfold measurements were available only for the Vale population. The results suggest that the higher average weight of those with ischæmic heart-disease is more likely due to muscle than to fat.

Physiological and biochemical factors (table IV).—The raised blood-pressure and the indirect maximum voluntary ventilation (M.V.V.) in those with ischæmic heart-disease have been previously described (Cotes et al. 1956). One point of interest is the decreased difference in systolic blood-pressure when the " electrocardiographic " rather than the " clinical " index is used. This was due to the difficulty of diagnosing ischæmic heart-disease in the presence of left ventricular preponderance, which led to disagreement between observers. Our findings about height are also of interest in relation to the higher M.V.V. in the group with ischæmic heart-diease. The increased height is found both for total height and stem height, and probably accounts for some of the difference in M.V.V. The data about cholesterol are being published elsewhere (Morris, to be published). The difference ($11 \pm 14{\cdot}6$ mg. per 100 ml.)

TABLE IV—PHYSIOLOGICAL AND BIOCHEMICAL CHARACTERISTICS

—		Vale of Glamorgan		Rhondda Fach	
		Ischæmic heart-disease	Others	Ischæmic heart-disease	Others
Average systolic blood-pressure (mm. Hg)	E.C.G.	168·3	160·1	156	145
	Clinical	180·8[2]	155·7	165·8[4]	139·4
Average diastolic blood-pressure (mm. Hg)	E.C.G.	96·3[1]	87·2	86	82
	Clinical	96·3	86·2	89·4[5]	80·7
Average M.V.V. (indirect) (litres per min.)	E.C.G.	101·7[3]	87·0	81·4	70·7
	Clinical	87·1	89·7	84·5[5]	65·8
Average blood-cholesterol (mg. per 100 ml.)	E.C.G.	260	249	..	..
	Clinical	256	250	..	..

1. Diastolic: $0{\cdot}02>P>0{\cdot}01$. 2. Systolic: $0{\cdot}002>P>0{\cdot}001$.
3. $0{\cdot}04>P>0{\cdot}03$. 4. Systolic: $P=0{\cdot}004$. Diastolic: $0{\cdot}04>P>0{\cdot}03$.
5. $P=0{\cdot}01$.

between those with and those without ischæmic heart-disease is small and statistically insignificant.

Family data.—The information in table V was obtained from the members of the samples at the time of the examination in the case of the Vale of Glamorgan, and two years later in the case of the Rhondda. Family size appears not to be correlated with ischæmic heart-disease, for the results differ in direction in the two surveys. The survival rate of the fathers of those with ischæmic heart-disease seems unexceptional: they appear to do rather better than the fathers of the controls. Conversely, the mothers of the ischæmic heart-disease group do rather worse than the mothers of the controls, but the differences are not significant. The most striking results come from the brothers and sisters. In every comparative pair there is a higher mortality among the siblings of the group with ischæmic heart-disease. The pairs where the differences are statistically significant are indicated in the table.

The causes of death of brothers and sisters have been investigated in both areas, but with such small numbers it is very hard to draw any conclusions as to the causes of the excess mortality.

Other factors.—In the paper reporting the survey of ischæmic heart-disease in the Rhondda Fach an attempt was made to test the hypothesis advanced by Morris et al. (1953) that hard manual work reduces the risk of developing the disease. The average number of years at the coal face in the two groups was compared, on the assumption

TABLE V—FAMILY DATA

—			Vale of Glamorgan		Rhondda Fach	
			Ischæmic heart-disease	Others	Ischæmic heart-disease	Others
Family size		E.C.G.	6·4	5·2	4·8	5·6
		Clinical	5·8	5·3	4·8	5·8
Survival of fathers	% dead	E.C.G.	91·7	97·8	100	100
		Clinical	94·7	90·9	100	100
	Average age at death	E.C.G.	69·1	68·5	69·7	63·6
		Clinical	69·0	68·5	67·3	59·0
Survival of mothers	% dead	E.C.G.	100	86·3	100	100
		Clinical	100	84·8	100	100
	Average age at death	E.C.G.	65·7	66·0	61·5	68·5
		Clinical	65·8	66·0	65·4	67·9
% of brothers dead		E.C.G.	36·8	28·4	63·2	42·0
		Clinical	40·0	26·2	60·6	38·3
% of sisters dead		E.C.G.	55·6[1]	20·7	52·6[2]	19·3
		Clinical	41·5	21·3	38·9[3]	18·2

1. $P<0.001$. 2. $P<0.01$. 3. $P=0.045$.

that coal-face work is on the average harder than other work in a mine; but no significant difference was found. The material has now been reanalysed using the " electrocardiographic " index. Those diagnosed electrocardiographically as having ischæmic heart-disease had worked for 5·7 years on the coal face compared with 16·9 years for the controls. The difference of 11·2 years is statistically significant ($0.005 > P > 0.001$). This, in general, supports Morris's hypothesis; but the results could be due to men with heart-disease leaving the coal face early, or to some other type of occupational selection.

We have also some information about mean chest diameter. This was measured on a high proportion of the miners and ex-miners in the Rhondda during the first Rhondda Fach survey. Using the clinical index, the mean chest diameters of those with and without ischæmic heart-disease was 27·8 cm. and 26·9 cm., and using the electrocardiographic index the figures were 28·1 cm. and 26·5 cm.

The material has also been analysed as regards smoking habits and social status (using the Registrar General's classification), but no significant correlations have emerged.

Discussion

Measurement of Prevalence

The essential difficulty in comparing the prevalence of ischæmic heart-disease in different areas is to avoid bias due to preconceived hypotheses. The electrocardiogram is the only suitable means of ensuring that such bias is eliminated. Tracings from different areas can be mixed and read by observers who are not told where they come from. In such circumstances the precise level of diagnosis of ischæmic heart-disease is relatively unimportant: since the criteria adopted can be assumed to be the same for all the tracings, comparisons between areas or between occupations will be valid. Hence we believe that our comparisons in the present paper are justified. On the other hand the wide variation in interpretation of electrocardiograms makes us sceptical of our absolute values for the prevalence of ischæmic heart-disease, and shows that much more work must be done before the findings of workers in different centres can be justifiably compared. Though the differences may disappear under the impact of the discussion caused by their measurement more basic research is likely to be needed. This will include the correlation of clinical and electrocardiographic findings with post-mortem findings on unselected groups, and the follow-up of large unselected populations to determine the relation between electrocardiographic abnormalities and expectation of life.

Ætiology of Ischaemic Heart-disease

A widely entertained hypothesis relates ischæmic heart-disease to the fat content of the diet and to the blood-cholesterol (Keys 1955, Bronte Stewart et al. 1955). There is evidence from many countries that people who live on diets low in animal fats tend to have a low mean serum-cholesterol level and little liability to ischæmic heart-disease (Keys and White 1956). While certain discrepancies in this hypothesis have been noted (Morris 1956, Yudkin 1957), the relevance of the blood-cholesterol to ischæmic heart-disease is supported by the observation at Framingham (Dawber et al. 1957) that people with a high total blood-cholesterol were more liable to an episode of ischæmic heart-disease.

In our investigation of men aged 55-64 the mean serum-cholesterol was insignificantly higher in those with ischæmic heart-disease than in the controls. This is at variance with the findings of Gertler and White (1954) in young adult males. Though racial differences between the groups studied—as demonstrated between Italians and Jews in the clothing workers' survey (Epstein et al. 1957)—might account for this discrepancy, a more probable explanation is that over the age of 55 we are dealing with a survivor population: those who had a high blood-cholesterol in their 30s and 40s had already died of ischæmic heart-disease. Alternatively, disordered lipid metabolism may be important mainly at younger ages. Biorck et al. (1957) concluded that, in people under 50 years old, the serum-cholesterol was higher in those with myocardial infarction than in normal controls, but over this age the difference was insignificant.

The differences in blood-pressure and maximum voluntary ventilation (indirect) have been discussed previously (Thomas et al. 1956, Cotes et al. 1956). Since then, Epstein and his coworkers (Epstein et al. 1957) have confirmed the raised blood-pressure in Italians with ischæmic heart-disease in New York, but not in Jews. As we have also found a significant relation between ischæmic heart-disease and body-weight, and weight is related to blood-pressure (Master et al. 1950), one must be cautious in drawing conclusions.

Our anthropometric results are of greater interest. Gertler and White (1954), who give a good summary of the literature, found that among young males those with coronary disease were significantly shorter and lighter. The striking difference between their results and ours is possibly explained by their dealing with young males. Alternatively, some bias may have been unintentionally introduced when selecting the 146 unmatched controls to compare with the 97 coronaries. Epstein (Epstein et al. 1957) apparently measured the heights of his population, but does not comment on any differences between those with and those without ischæmic heart-disease.

As regards our family data, the situation is somewhat similar. Here too the literature has been well summarised by Gertler and White (1954). They found that the parents of people with ischæmic heart-disease had a higher mortality than the parents of controls. For this purpose their material was more suitable than ours, since the younger age-group made the measurement more sensitive. They also found a higher mortality among the siblings of the controls (20%) than among siblings of the coronary group (15%), though the difference was not significant.

We, on the other hand, found a significantly higher mortality among the siblings of those with ischæmic heart-disease. Our data agree with theirs in showing no significant difference in the size of family in the two groups. For this study our age distribution is more suitable.

Faced with these divergent results we can only conclude that further work is required on similar populations, particular care being paid to the choice of controls.

Summary

1. Comparison of the prevalence of ischæmic heart-disease in different places presents certain difficulties.

2. The technique of random sampling from a population, accurately defined by private census, is illustrated by two surveys of men aged 55-64. The findings in a sample of 55 miners and ex-miners living in the Rhondda Fach are compared with the findings in a sample of 100 men who had never worked in dusty occupations, living in the Vale of Glamorgan.

3. Three cardiologists independently read the electrocardiograms from each subject, and their findings varied considerably. Hence, though the comparison of the two areas may be regarded as valid, the absolute prevalence values should be treated with reserve.

4. Two indices of ischæmic heart-disease have been used:

(1) The clinical index, based on clinical assessment, electrocardiography, and radiography, by one cardiologist.

(2) The electrocardiographic index, based on agreement between three cardiologists that an electrocardiogram showed changes compatible with the diagnosis of ischæmic heart-disease.

The prevalence in the two areas was:

Clinical index: Vale 25·0%, Rhondda Fach 38·3%.
Electrocardiographic index: Vale 17·0%, Rhondda Fach 21·3%.

Though the mining group seemed to have a somewhat higher prevalence the difference was not statistically significant.

5. Those diagnosed as having ischæmic heart-disease were both taller and heavier than the others.

6. The siblings of the men with ischæmic heart-disease had a higher mortality than the siblings of the controls.

7. No significant difference was found in the mean serum-cholesterol levels of the two groups.

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TREATMENT OF SEVERE HEAD INJURIES

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THE very severe head injury, complicated or uncomplicated by surface hæmorrhage, has always been the cause of grave concern to the neurological surgeon. It has been noted that patients with cerebral lesions die in a characteristic way, and Jefferson (1944) wrote:

"It is the fate of all of us to watch patients with cerebral lesions dying from something characterised by tachycardia, and cardiac irregularity, from upsets of thermal regulation, from metabolic upsets which we have not yet found a means to study properly, from something that bears the hallmarks of a disease process as much as, say, pneumonia."

The distinguishing characteristics of the group of cases of head injury to be described here were a partial or complete decerebrate posture with tonic fits and a rapidly rising temperature. Other signs of autonomic disturbance were usually present, but fell into no clear-cut pattern likely to be useful in routine diagnosis. Kinnier Wilson (1920) described the association of this syndrome with lesions of the upper brain-stem and pointed out its resemblance to the effects of experimental transaction at the level of the superior colliculus in animals. Other observers have confirmed and amplified Wilson's description.

When the syndrome arises after head injury, it is probably the result either of intrinsic damage to the upper brain-stem, or of a mid-brain shift following a rise in supratentorial pressure. When it arises as a secondary effect of raised pressure, it occurs late in the process of descent and indicates considerable damage amounting to partial or complete transection, which is not always reversible. The signs arise from the paralysis of some structures and the action in isolation of others.

Several types of herniation of supratentorial structures into the incisura have been described (Meyer 1920, Vincent et al. 1936, Azambuja et al. 1956), all of which eventually compress and distort the brain-stem or imperil its blood-supply. The mechanics of these processes have been well reviewed by Johnson (1957), who points out that, while compression is often worst at the level of the incisura, structure must be distorted at all levels, and that, whatever the pattern of movement, when the pressure is supratentorial the whole brain-stem will shift down. This downward shift may be sudden and catastrophic; but on the other hand it may be gradual, and in the latter case there may be little clinical evidence of the shift until a final and comparatively small further displacement leads to fatal compression.

It is difficult clinically to identify accurately the causes of swelling of the brain in any given head injury, but morbid-anatomical and experimental evidence suggests that it is due to a combination of hæmorrhage, local œdema, and hyperæmia with the effects of hypoxia, carbon-dioxide retention, and "acceleration concussion".

Hæmorrhage is often found, and if massive may be the principal cause of displacement. Of the cases to be described, in 27 out of 56 in the control series and in 15

out of 26 in the treated series, such hæmorrhage, subdural or extradural, was present. Local œdema or its histological effects may be demonstrated in close proximity to lacerations of the brain and sometimes very near to the anterior part of the lateral ventricle. This is likely to be only a contributory factor, as it occurs rarely if ever in a massive and generalised form (Greenfield 1938).

Hyperæmia of the brain is found at necropsy after concussion and has been so produced experimentally in cats. White et al. (1942) demonstrated hyperæmia of the brain in cats after inhalation of increased concentrations of carbon dioxide, and swelling of brain substance not due to hyperæmia in conditions of severe hypoxia. Davies and McKinnon (1949) have shown the importance of the combined effect of hypoxia and hypercapnia in producing cerebral hyperæmia in man. There is experimental evidence that generalised swelling of the brain which cannot be accounted for by hyperæmia, or correlated directly with water content, occurs after acceleration concussion. White et al. (1943) recorded increases in brain volume of up to 5% in cats concussed by the method of Denny Brown and Ritchie Russell (1941).

When a brain-stem shift has occurred, other mechanisms come into play. Compression or angulation of the brain-stem can obliterate the aqueduct, causing internal hydrocephalus. Trapping of the transtentorial veins in the incisura will cause a rise of venous pressure and impede cerebral blood-flow.

Johnson (1957) has drawn attention to the role of respiratory embarrassment in exacerbating downward displacement of the brain-stem by causing distension of intracranial veins. Patients with severe head injuries commonly inhale mucus, vomit, and blood soon after injury, particularly if transferred to hospital in the supine position, and pooling of mucus in the pharynx is often observed. Apart from these mechanical factors, midbrain dysfunction itself leads to disorderly respiration. In both cases venous pressure inside the skull must fluctuate considerably, and some observations made during the present series point to the importance of respiratory disorder as a precipitating cause of coning.

3 patients in the series were admitted in a state of cerebral irritation and coma without focal signs, passed through an episode of mechanical respiratory obstruction, and then assumed a decerebrate posture with rising temperature. Subdural hæmatomas were discovered at craniotomy in all 3 cases. In these cases the appearances suggest that a large downward displacement existed with few clinical signs until a further slight descent provoked by the respiratory upset tipped the balance and produced a pressure cone.

The role of respiratory insufficiency in the mortality of severe head injuries has been discussed by Maciver et al. (1958), who outlined the regime which we have adopted, since Dec. 13, 1956, in the treatment of such cases. The most important features of the treatment are as follows:

1. Correct posture to prevent seepage into the lungs and tracheobronchial tubes.
2. Isolation of the lungs from the disorganised pharynx by early tracheotomy.
3. Their further protection by continued aseptic tracheobronchial toilet.
4. The use of a lytic cocktail to coordinate the reticular mechanisms of the brain-stem, and control rigidity, restlessness, and hyperthermia.
5. Avoidance of oral feeding during unconsciousness.
6. Maintenance of physiological tensions of oxygen and CO_2 in the blood.
7. Maintenance of fluid and electrolyte balance and calorie intake.
8. Combating of infection by use of antibiotics.
9. Relief or prevention of secondary cerebral œdema by use of intravenous triple plasma.

We describe here the details of treatment, the difficulties we have encountered, and the progress we have made. Of 83 cases in the present series, 26 were treated by the regime described.

Clinical Features

The clinical picture varied according to the degree of damage or compression to the brain-stem. The best prognosis attended the cases showing hyperpyrexia with tonic fits superimposed on decerebrate rigidity. The poorest prognosis was present in the cases which showed complete thermolability and absolute flaccidity save when disturbed by feeble tonic fits. Medullary failure was imminent in the thermolabile and flaccid group, the blood-pressure falling and the respirations becoming shallow, irregular, and gasping. However, 2 patients with this clinical picture have survived. The tendon reflexes are increased in the hyperpyrexial and rigid patients; the plantar reflexes are extensor, whereas in the flaccid state neither tendon reflexes nor toe movements can be elicited.

In the fully developed decerebrate state the patient lies with knees and toes rigidly extended and the ankles

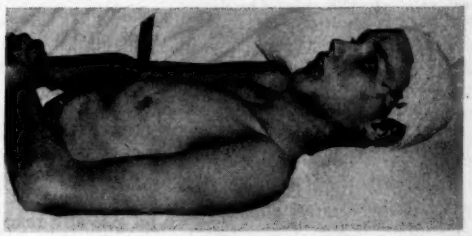

Fig. 1—Patient five days after severe head injury, with decerebrate rigidity and hyperpyrexia.

plantar-flexed. There is spasm of the femoral adductors and pectorals, the arms are pronated and the wrists flexed, while the elbows are held in a position peculiar to that patient which may be either flexion or extension (fig. 1).

Tonic fits, which are merely exacerbations of the spasm described, may be continuous or intermittent. They are always associated with a rise of temperature and may be precipitated by external stimulation. Partial or fragmentary forms of the decerebrate posture were seen. During their recovery 2 patients still showing decerebrate rigidity and pyrexia were able to speak and move the spastic limbs purposefully.

A tachycardia of 100–160 developed in all cases within an hour of onset of decerebrate rigidity. The breathing was stertorous and the neck veins were distended. The patient seemed unable to clear mucus, blood, or vomit from the pharynx (Denny Brown and Ritchie Russell [1941] noted a transient disorder of swallowing mechanisms in concussed cats). In the acute head injury, damage to the vagal nuclei is also partially responsible for this difficulty. Vomiting is frequent and usually contains altered blood—sometimes blood previously swallowed but sometimes arising from gastric or œsophageal erosions, which are a common postmortem finding in head injuries of this severity (Maciver et al. 1956). No case of ruptured œsophagus occurred in the treated group, but 2 cases

occurred in the control series. Absence of bowel sounds were recorded often, abdominal distension occasionally, and retention of urine twice.

The pupils were unequal in 16 cases, equal in 6, obscured by orbital hæmatoma in 2, and masked by 3rd-nerve damage in 2. They were reduced in size in most instances and fixed in 19 cases. The eyeballs were usually central, but roving movement once, and conjugate deviation twice, have been observed. These findings relate to the first examination of the patients.

Stage of Coma (one to three weeks)

The signs are a mixture of those due to injury and those due to therapy. Muscle hypertonicity is reduced and tonic fits do not occur, the temperature being held steady at 96–98°F. Respiration is quiet and free from straining. The blood-pressure is usually low on chlorpromazine and tachycardia is constant. Weight loss and normochromic anæmia are usual. Skin-sensitivity reactions to chlorpromazine and penicillin are often seen; profuse diarrhœa occurred in 4 cases in which tetracycline had been administered. The signs of developing bronchopneumonia at this stage are ominous.

Stage of Cerebral Irritation

The patient begins to move his limbs purposelessly and thresh around in bed, often screaming in a nerve-racking way. The eyes are open and soon appear to be following movements. As recovery progresses, movements become more purposeful and noises more like words. Pupil size and reactions are normal, and tendon reflexes present and equal in the absence of focal damage, though plantars are often extensor. Exceptionally, the decerebrate attitude persists partially (fig. 2). Towards the end of this period the patient begins to talk irrationally and can sit up in bed with assistance. The tracheotomy has usually healed.

Fig. 2—Patient in control series showing persistent decerebrate attitude three months after severe head injury in which brainstem was primarily involved.

Stage of Confusion (two to twelve weeks)

This period covers the piecemeal return of mental faculties together with the ability to stand, balance, walk, feed, and make use of the toilet. Ability to talk comes early—on the average three weeks after injury—but rational conversation much later. The patient is disorientated, often failing to recognise family and friends, and can develop extraordinary delusions to account for his condition and circumstances. The average time for walking was six weeks, but 1 patient was mobile after a fortnight. When physical recovery outstrips mental, a formidable nursing problem presents. The appetite is always excellent and usually ravenous, and weight is rapidly regained. Formal neurological examination and assessment of deficit are possible.

Treatment

The regime laid down is in no way a substitute for accurate diagnosis and surgery—rather the reverse, for it places within the scope of surgery cases in which the prognosis would otherwise be hopeless. A decerebrate picture in a case of acute head injury was always thought in the past to be an unequivocal sign of an injury to the mid-brain. In some cases presenting with similar signs, a surface hæmorrhage has been found at operation or at necropsy; Jefferson (1921) drew attention to this fact and suggested that, in any case where a doubt exists, exploratory burr-holes are advisable. We would further suggest that routine burr-holes are always advisable to exclude surface collections, particularly subdural hygromas and hæmatomas.

Immediate Treatment on Admission

Although speed is not always of prime importance, there are occasions where it is life-saving. Where a patient is admitted deeply unconscious in a decerebrate state with inadequate respiratory effort and a rapidly rising temperature, the pupils, long bones, ribs, pelvis, spine, abdomen, and chest should be rapidly examined to exclude fracture, pneumothorax or hæmothorax, and intra-abdominal bleeding.

The clothing should then be removed and a drip set up at the ankle. 400 ml. of sterile water should be mixed with dried plasma of 3 pints of blood, and run as fast as the drip will allow, a specimen of blood for cross-matching being obtained at the same time. 25 mg. of chlorpromazine should be injected into the drip, thus bringing about relaxation in approximately a minute. As soon as the jaw relaxes an endotracheal tube should be passed under direct vision, and suction of inhaled blood or regurgitated stomach contents should be instituted, and warm, moist oxygen given. A stomach-tube should be passed and the stomach emptied, the tube being retained for further aspirations. The head is then shaved and any fractures of the limbs are immobilised. The question of tracheotomy and of operation is then discussed, and if this is necessary, it is arranged as soon as the patient's condition is reasonably satisfactory; and as soon as possible regular doses of lytic cocktail are given, usually by drip or by intramuscular injection. Apart from triple plasma, blood in our opinion is the only isotonic fluid permissible, and it is given only where associated injuries would necessitate transfusion.

The first case treated along these lines was a boy of 16 years, admitted in decerebrate rigidity an hour after being knocked down by a car. On admission his temperature was 105·4°F and he was in circulatory failure with Cheyne-Stokes breathing. Normally we would have expected death within half an hour, but the use of intravenous triple plasma and intravenous chlorpromazine, exposure to cold air with wet sheets, and the passage of an endotracheal tube changed the picture immediately. Within an hour the temperature was brought down to normal and the decerebrate condition was under control. When the endotracheal tube was removed a few hours after admission, his condition immediately deteriorated; he became blue and obviously anoxic, and his decerebrate rigidity returned. His tube was replaced with immediate improvement, and tracheotomy was carried out as soon as possible with continuing improvement in his condition. After five weeks of coma he began to make a satisfactory recovery.

Posture

It is important, until at least an endotracheal tube is passed and the stomach contents aspirated, to nurse the patient in the semiprone position with a Trendelenburg

tilt of 20°, or even in a knee-elbow position where there is a drainage of blood and cerebrospinal fluid into the mouth and pharynx. Once, however, the patient is intubated or tracheotomy has been performed and the regime commenced, we are of the opinion that the best position for nursing is the supine position without pillows initially, the position being frequently changed, and before suction the patient is placed in the Trendelenburg position for ten minutes to effect adequate drainage. All other positions appear to embarrass respiration. After suction the patient is returned again to the supine position. As the patient progresses a sitting position can be gradually adopted.

Tracheotomy

In the deeply unconscious patient suffering from the effects of a severe head injury, cerebral anoxia is likely to produce profound and irreversible changes in the brain-stem and cerebral hemispheres. In our opinion tracheotomy is the only certain method in the prevention of cerebral anoxia, and in all adult patients it has been our practice to perform this operation as quickly as possible. As has been already indicated, inserting an endotracheal tube may be of value as an emergency procedure, or if early return to consciousness appears likely, but in our opinion no tube should be retained for longer than eight hours. In children tracheotomy may not be as necessary but should be performed at once if indicated. Of 21 adults in this treated series 20 had tracheotomies; but of 5 children only 2 had this operation performed. Once tracheotomy has been performed careful aseptic suction must be applied frequently, and the tracheal tube and bronchial tree must be kept clear. This suction must be adequate but reasonably gentle, and the suction tube should be soft enough to ensure that damage to the lining of the bronchial tree is minimal. The tube should also be long enough to reach to the depths of the tree when required, suction first being applied on one side and the patient then turned so that suction can be applied to the other bronchus. Any oxygen administered should be warmed and moistened so that hardening or coarsening of the secretions is avoided.

The Lytic Cocktail

This cocktail, consisting of chlorpromazine, promezathine, pethidine, and levallorphan, has been used in all cases, but no attempt has been made to produce hypothermia or a hibernating condition.

The cocktail has the following functions:

1. It has made it possible to control temperature with comparative ease, and our aim is to maintain as normal a body temperature as possible.

2. It relieves muscle spasm and abolishes tonic fits, thereby reducing heat production and oxygen consumption.

3. Vomiting is reduced or abolished by chlorpromazine, whilst gastric secretion and intestinal mobility are both markedly reduced; and there is a hope that autonomic disturbance, ulceration and rupture of the œsophagus, or mucosal hæmorrhage may be prevented. Drying of secretions in the mouth and respiratory tract, though a troublesome side-effect in the conscious patient, is highly desirable in the decerebrate state.

4. It enables intubation to be carried out without using a relaxant.

5. It markedly reduces restlessness.

6. It has been found to protect animals against traumatic and hæmorrhagic shock, and Pocidalo and Tardieu (1954) found that it increased survival-time or diminished the severity of lesions produced in dogs by injecting irritant materials into the cerebral peduncles.

Dosage.—Usually each dose of the cocktail contains 25 mg. of chlorpromazine, 25 mg. of promezathine, 25 mg. of pethidine combined with levallorphan; the daily requirement of each of the first three constituents varies from 100 to 300 mg. according to the severity and progress of the case. In certain circumstances the dosage of one of the constituent drugs has been altered—e.g., if the patient is reacting to slight external stimuli by violent tonic fits, it would be reasonable to increase the dosage of pethidine and levallorphan. The cocktail is given at first by intravenous drip in urgent cases, or more usually by intermittent intramuscular injection. It is possible to produce complete flaccidity in all cases if a large enough dose is given, and it may be useful to do this initially so that the temperature can be reduced from dangerously high levels; but such doses appear to depress the respiration and may lead to hypostatic pneumonia if used continuously. It has, therefore, been our object to give a sufficient dosage greatly to reduce, but not to abolish, abnormal tone. At this level the temperature will have to be controlled physically; this is a relatively easy matter.

Complications.—The only constant complication encountered, which was definitely due to chlorpromazine, was drug rash. In the final stage of this regime almost all patients suffered hypotensive attacks lasting twelve to twenty-four hours. These were predominantly systolic falls of 20–40 mm. Hg, but 6 patients required mephentermine or noradrenaline for short spells. These attacks may have been due to the chlorpromazine, but at this stage we were using pethidine without levallorphan, and since changing over to this combination we have had no further trouble. We felt that pethidine alone produced a degree of respiratory depression which led to a fall in blood-pressure due to further anoxia of the medullary centres. Pethidine and levallorphan appear to be completely safe, and, of course, no respiratory depression is produced. Laborit et al. (1955) believe that chlorpromazine causes a shift of intracellular potassium into the cells, and a lowered serum K^+ was a fairly constant finding in the treated group, though in no case did the level fall dangerously low. No severe disturbance of respiratory rate and rhythm was noted after intravenous injection of chlorpromazine in decerebrate cases; in fact return to a more normal state was the rule, although Dobkin et al. (1954) have noted irregularity of rhythm with decreased minute volume.

Cooling

If sufficient doses of the lytic cocktail are given there is little difficulty in lowering the temperature by: (1) exposure of the patient with, if necessary, an open window or door; (2) the use of wet sheets; (3) strategic placing of ice-filled rubber bags; and (4) using the more complex circulating coolers. Cooling of the injection site should be avoided, and heavy cooling devices should not be allowed to press on the chest as this reduces tidal volume.

Feeding

This should be intravenous until danger of regurgitation and aspiration is over; this period lasts usually one to four weeks. All intravenous fluids are made hypertonic in the first week by adding 50% dextrose or sucrose. After this period a stomach tube is used until the patient has recovered sufficiently to feed himself. Initially during this period a constant drip of milk and water is given, and this is followed by a once-daily tube feed yielding

2200 calories (protein 100 g., fat 100 g., carbohydrate 225 g.) with the following ingredients:

Whole milk	40 oz.
Eggs	2
Full cream dried milk	3 oz.
Soya flour	2 oz.
Glucose	4 oz.
Salt	gr. 2·5
Ferrous sulphate	gr. 3
Aneurine hydrochloride	5 mg.
Riboflavine	2 mg.
Nicotinamide	20 mg.
Pyridoxine	2 mg.
Calcium	3 mg.
Ascorbic acid	200 mg.
Vitamin A	4500 I.U.
Vitamin D	1000 I.U.

Once the patient's tracheotomy is closed he is given small doses of water by mouth, increasing to milk-and-water mixture and then to a high-protein and high-vitamin diet.

Oral feeding is most dangerous because of the incoordination of swallowing mechanisms, and if the patient is encouraged to swallow too soon aspiration into the trachea often ensues.

Electrolytes

These should be estimated daily at first, particular attention being paid to serum-potassium. A reduction of potassium has been a constant finding, and within twenty-four hours it falls to 8–14 mg. With reference to the blood picture 10 out of 16 adults who lived long enough developed anæmia with 10 g. Hb per 100 ml. or less. Hæmoglobin was estimated frequently and, when necessary, blood was transfused.

Antibiotics

The bronchial secretion should be repeatedly examined bacteriologically as a guide to the choice of antibiotics. Penicillin has usually proved sufficient if given in large doses (1 million units intramuscularly four-hourly). Tetracycline appeared to be very dangerous in 3 cases. In the treated group 4 patients who received tetracycline developed profuse and persistent diarrhœa; all had received large doses of vitamins and in no case were pathogenic organisms isolated from the stool. 3 of these patients became considerably dehydrated and showed a severe increase in the blood-urea. We are of the opinion that, if possible, use of tetracycline should be avoided.

Hypertonic Plasma

Intravenous hypertonic fluids cause a fall in the cerebrospinal-fluid pressure, and there is clinical evidence that they can improve the condition of patients with raised supratentorial pressure. Hughes et al. (1938) introduced hypertonic plasma in an attempt to produce a more sustained effect than that produced by non-colloidal substances and to avoid the rebound to higher pressures. They claimed that a sustained fall of pressure can be produced in man, and this was confirmed in animal experiments by Bond et al. (1938). We have departed from this method only by giving much larger quantities of plasma solids, 400 ml. of sterile water being mixed with dried plasma of 3 pints.

The uses of hypertonic plasma are: (1) to prevent cerebral œdema, (2) to treat surgical shock, and (3) to reverse coning. Pupils which had become fixed and dilated have become normal in size and reaction within fifteen minutes of a drip being started, with a corresponding improvement in respiration and pulse-rate.

Concentrated plasma has been used in fatal cases, and at necropsy the brain has appeared much less swollen than in our previous cases where intense dehydration has been brought about by means of restricted fluid intake and mercurial diuretics. No serum jaundice or other toxic effects attributable to plasma have been observed. In vitro, human red blood-cells incubated in triple-strength plasma at 37°C for an hour showed no hæmolysis or other damage.

Results

The control series was collected in retrospect from case-records. The dangers of this procedure are appreciated, but some standard for comparison is desirable, and it is difficult to withhold treatment which appears to benefit the patient for academic reasons, however sound.

All head injuries admitted under the care of two of us (I. N. M. and L. P. L.) between Jan. 1, 1955, and Dec. 11, 1956, were reviewed using the same diagnostic criteria as in the treated group—i.e., partial or complete decerebrate rigidity with tonic fits and a rising temperature. Of 1092 case-records considered, 56 fulfilled the criteria of selection and form the control group. The treated group of 26 patients was drawn from a total of 413 consecutive admissions. The difference in incidence in the two groups is not significant; so the figures can be pooled for a better estimate, giving for the syndrome an incidence of 5·5% of all head injuries.

As a further check on sampling, the incidence of severe associated injuries (other than to the head) was compared in the two groups. Such injuries occurred in 10 of the 26 patients in the treated group (38%) and in 16 of the 56 patients in the control group (28%): this difference is not significant ($\chi^2 = 0{\cdot}55$ with 1 df.), suggesting that the groups were comparable with respect to the violence of injury. Clinical signs other than those used for selections were generally similar in the two groups, but there was a considerable difference in age distribution, the control series containing 19 more children and 3 patients over 61 years. To get around this difficulty a "standardised" control group was constructed by applying the death-rates partitioned by age and sex in the crude control group to a hypothetical population with the same age and sex distribution as the treated group.

Mortality

Table I shows the mortality in the control and treated groups (see also fig. 3).

TABLE I—MORTALITY IN CONTROL AND TREATED GROUPS

Group	Died	Recovered	Total	Mortality (%)
Crude control	39	17	56	69·6
Standardised control	20	6	26	76·8
Treated	10	16	26	38·4

χ^2 between crude control and treated group = 4·7 with 1df.
χ^2 between standardised control and treated group = 6·4 with 1df.

Mortality in the treated group was 38·4%, in the crude control group (which contained a high proportion of children) 69·6%, and in the standardised control group 76·8%. The difference between the mortality-rates in the treated and standardised control group is statistically significant ($\chi^2 = 6{\cdot}4$).

Because of the diversity of type of associated injury and consequently small numbers of each type recorded, detailed comparison of effects has not been attempted. However, of those 18 patients in the control group who had no severe associated injury, 6 died, compared with 4 deaths in the 8 who had severe associated injury.

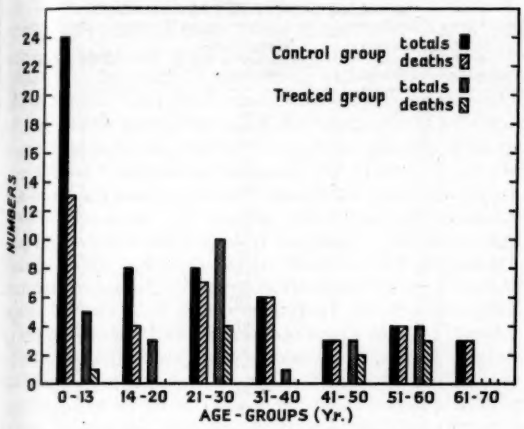

Fig. 3—Mortality in control and treated groups.

Survival-times

The survival-times of patients who died in the treated and control groups are shown in fig. 4 and in table II.

TABLE II—SURVIVAL-TIMES: MEDIAN TEST

—	Control	Treated	Total
Above median	16	8	24
Below median	23	2	25
Total	39	10	49

χ^2=3·4 with 1 df. (i.e., falls just short of 5% level at 3·8).

Those in the treated group survived longer than those in the control, and by the median test this difference is found to fall just short of significance at the 5% level.

The degree of residual disability in those who recovered was assessed during inpatient treatment and at follow-up clinics. Of 56 patients in the control group, 17 survived: 10 made a good enough recovery to pass as normal; 1 showed a personality change which made him "difficult to manage"; 3 were left with a hemiparesis, and 2 of these had, in addition, homonymous hemianopia and a severe speech defect. The 3 worst results were in patients described in follow-up notes as "completely paralysed", "paraplegic, blind, and totally aphasic", and "a complete vegetable". These observations were made at one to two years after injury, when some of the patients were still improving slowly.

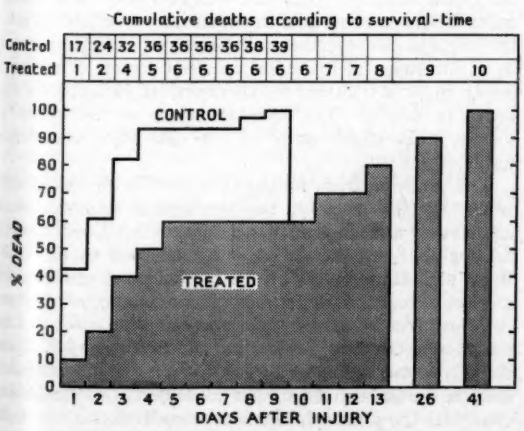
Cumulative deaths according to survival-time
Control 17 24 32 36 36 36 36 38 39
Treated 1 2 4 5 6 6 6 6 6 6 7 7 8 9 10
CONTROL
TREATED
% DEAD
DAYS AFTER INJURY
1 2 3 4 5 6 7 8 9 10 11 12 13 26 41

Fig. 4—Survival-times in patients who died.

In the treated series, 16 patients recovered out of a total of 26.

Follow-up of Patients in the Treated Group

All of the surviving patients in this group are under constant observation and have been submitted to psychological testing at regular intervals.

Mental state.—2 women have shown fairly pronounced mental changes for some time.

One of these, a young married woman of 21, had an intellectual function below average, and there was difficulty in assessing her premorbid intelligence up to February of this year. Since then, however, she has made remarkable progress and is now running her own house, and doing her own cooking and shopping, and her memory improves steadily.

The other woman, a girl of 19, was very confused and violent for some time. Her weight has increased enormously and she is walking well. She is unable to read, and mentally, at first sight, she will pass for normal; but under close questioning it is obvious that she is slow in understanding, and we are of the opinion that there is a real deterioration in her intellect, though according to her mother (who has always proved a reliable witness) the girl is improving rapidly.

1 man is somewhat euphoric and a little childish but is extremely good-tempered and works well.

Physical defects.—Relatively few have any physical or neurological deficit apart from the cases mentioned. One man is left with definite right facial weakness, and has slight difficulty in eating and speaking because of contracture of his facial muscles. He has also lost his sense of smell completely. Another man is left, so far, with a permanent 3rd-nerve palsy. One woman has a moderate residual left hemiplegia, which is steadily improving, and she is managing well. One man has shown a fair amount of irritability and poor memory for recent and past events and has slight weakness of the left leg. He also complains of dizziness.

Return to work.—5 patients have not yet returned to work. At present 2 of these are considered fit for light work but have not yet returned. 1 is likely to be fit for light work in a month and another in three months. 2 patients have returned to light work, and both should return to their normal employment within a reasonable time. 9 patients have returned to their pre-accident occupation and are managing well. Important factors influencing prognosis are the age and sex of the patient. Children have the lowest mortality and make the best recoveries; this may be because they are less prone to respiratory insufficiency. Women also seem better able to survive severe head injuries than men, the survival-rate being 5 out of 9 in the control series and 6 out of 6 in the treated series. The injuries in these cases were comparable in severity to those in the men.

Conclusions and Summary

After a severe head injury, decerebrate rigidity and hyperpyrexia, either separately or together, must be regarded as an ominous development. A retrospective survey showed that in this type of case the mortality was 77%.

Respiratory insufficiency has been treated by immediate tracheotomy and aseptic tracheobronchial toilet, and rigidity and hyperthermia by the use of the lytic cocktail and cooling. Cerebral œdema has been prevented or relieved by infusion of hypertonic plasma.

The mortality has been reduced to 38·4%, and this difference has been shown to be statistically significant.

With further improvements in technique the mortality could possibly be lowered to 20%, but this will not be achieved unless it is realised that respiratory insufficiency exists from the time of the accident, and steps are immediately taken to counteract it, both during transportation to a hospital or head-injury centre and on arrival at a casualty department.

It is likely that in the treated group a high proportion of patients would have died if these recent methods of treatment had not been adopted. With the regime described, the majority of patients who recovered have developed little in the way of intellectual deterioration or severe mental symptoms. Most of the patients will be fit to return to productive work and will not remain a burden on their family or the community.

Our thanks are due to Mr. I. J. C. Frew, consultant ear, nose, and throat surgeon, Newcastle General Hospital, for his assistance in our cases and for performing all the tracheotomies at any hour of the day or night; and to Dr. J. G. Matheson and Dr. J. D. Whitby, consultant anæsthetists, Regional Neurosurgical Unit, Newcastle General Hospital, for the interest they have shown and for their considerable assistance. But for the magnificent nursing these results could not have possibly been obtained. We should like to thank our ward sisters—Miss W. Gault, Miss E. Brooks, and Miss I. Shearer—for all their help, and the following staff nurses: Miss M. Laidlaw, Miss B. Brown, and Miss D. J. Jerdan, who constantly attended our patients. This type of treatment puts considerable strain on all the staff concerned, and our thanks are also due to our theatre sisters—Miss E. Hetherington, Miss M. White, and Miss V. Marley—who have helped us in no uncertain fashion. Our thanks are due to Dr. S. G. Owen and Mr. Hubert Campbell, who gave helpful advice on the analysis of the results.

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COLOUR INDEX IN NORMAL SUBJECTS

AS DETERMINED WITH THE AID OF AN AUTOMATIC RED-CELL COUNTER

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THE construction, calibration, and performance of an automatic red-cell counter have been described elsewhere (Macfarlane, Payne, Poole, Tomlinson, and Wolff 1958). The object of constructing such a machine was to make accurate and precise red-cell counts a practical possibility in a routine hæmatological laboratory. The main purpose of such counts is to make accurate estimates of the amount of hæmoglobin per cell. In severe cases of iron deficiency or megaloblastic anæmias this ratio (which can be expressed either as the colour index or as the mean corpuscular hæmoglobin) shows large deviations from the normal value; but because of the great errors of visual red-cell counting (and, until comparatively recently, of hæmoglobinometry) little is known about the variation in the colour index among normal human subjects. Such information is required before one can assess the significance of small changes in the colour index, now detectable for the first time.

The results of colour-index determinations in 24 normal subjects are here reported.

THE COLOUR INDEX OF 24 NORMAL SUBJECTS

Red-cell count (millions of red blood-cells per c.mm.)	Hæmoglobin (percentage of B.S.I. standard)	Colour index
4·96	99	1·00
4·90	97	0·99
5·58	108	0·96
5·21	106	1·02
4·86	98	1·01
5·05	100	0·99
5·01	102	1·02
4·81	95	0·99
4·46	86	0·97
4·82	99	1·03
4·94	103	1·04
4·96	100	1·01
5·24	100	0·95
5·36	98	0·91
4·85	98	1·01
5·84	107	0·91
5·24	97	0·92
5·17	93	0·90
4·67	88	0·95
5·16	97	0·94
5·01	103	1·03
4·66	97	1·04
4·55	95	1·04

Investigations

Methods.—Blood obtained by venepuncture was run directly into glass bottles containing Wintrobe's oxalate mixture in dry form, and mixed well. Red-cell counts were made with the apparatus described by Macfarlane et al. (1958) and hæmoglobin estimations with an M.R.C. photometer (King et al. 1948). The actual photometer used was one in use in the routine hæmatology laboratory of the Radcliffe Infirmary. Its calibration is checked frequently and its accuracy can be relied upon.

The subjects were adults of either sex. Because of the small variation in the results for the whole series there was no advantage in classifying them in any way.

Results.—The table shows the red-cell counts, hæmoglobin levels, and colour-index values. Red-cell counts are expressed as the number of cells per c.mm. of blood and hæmoglobin levels as percentages of the B.S.I. Haldane hæmoglobin colour standard (B.S. 1079: 1942; see Donaldson, Harding, and Wright 1943). The colour index has been computed in the usual way as the ratio of the hæmoglobin percentage to the red-cell count expressed as a percentage of 5 million cells per c.mm. The mean colour index is 0·99 and the coefficient of variation for the series is 4·93%. The standard error of the mean is 0·0099. The mean value of 0·99 has 95% confidence limits of $\pm 2\%$.

The variation from subject to subject is obviously very small. If the error of the mechanical red-cell count contributes a coefficient of variation of 2·5% and that of hæmoglobin estimation 1·6% (Macfarlane et al. 1958, Biggs and Allington 1951), the coefficient of variation for a series of colour-index measurements would be expected to be at least 3% if there were no sampling error and no variation from one subject to another. As the figure actually found in this series was 4·9% it can be concluded that the variation from subject to subject is so small that, even with the precise instruments now available, it cannot be estimated with any useful degree of exactitude.

Discussion

The fact that the mean colour index for normal human subjects turns out to be very close to unity, when determined by the methods described above, is a fortunate coincidence. There is no theoretical reason why it should. We can now infer that the B.S.I. hæmoglobin standard corresponds closely to the hæmoglobin content of blood containing 5 million normal red cells per c.mm. It was not intended to do so when it was set up. Donaldson et al. (1943) aimed at reproducing the colour of Haldane's original carboxyhæmoglobin standard (Haldane and Smith 1900, Haldane 1901). Haldane had prepared a standard supposed to represent the mean level for healthy males. There is no reason to suppose that Haldane failed in his object, but there is reason to doubt whether Donaldson et al. reproduced the colour of Haldane's original standard. Be that as it may, the B.S.I. standard is now known to be about 7% below the mean level for healthy males (King et al. 1944) and must be regarded as arbitrary. If the mean normal colour index had turned out to be much below or above unity the question would have arisen as to whether it might be expedient to redefine 100% of hæmoglobin. Fortunately no such redefinition is either necessary or desirable.

Some clinical pathologists prefer to express the ratio of the hæmoglobin content of blood to its red-cell count as a weight of hæmoglobin per cell (the " mean corpuscular hæmoglobin ") rather than as the colour index. No additional information is supplied in this way, since the mean corpuscular hæmoglobin is in effect derived from the colour index by multiplying by a constant. This constant involves a conventional figure for the hæmoglobin equivalent of the B.S.I. standard. As has been argued elsewhere (Poole 1954) the conventional figure at present generally employed is almost certainly inaccurate. Moreover, if a result is reported as the mean corpuscular hæmoglobin, the recipient of the report must know what the normal figure is before he can interpret the significance of any particular figure which may be given. In other words, he must mentally convert the mean corpuscular hæmoglobin into the colour index, a step which could have been avoided by reporting the colour index directly.

Notwithstanding these considerations, the decision as to whether to report results as the colour index or the mean corpuscular hæmoglobin must in practice be dictated by local preferences. In the series reported above the mean value for the mean corpuscular hæmoglobin is 29·4 micromicrogrammes if the hæmoglobin equivalent of the B.S.I. standard is taken as 14·8 g. per 100 ml. of blood, or 28·9 μμg. if the equivalent is taken as 14·5 g. (Poole, 1954). This is very close to the figure of 29·0 μμg. given by Wintrobe (1934), which was the mean of 698 determinations on adults of either sex and which he still regards as the best available estimate (Wintrobe 1956).

The constancy of the colour index in different normal human subjects is striking. Because of the errors of the visual red-cell count, previous information on the variation between different normal subjects is of little value: indeed Biggs and MacMillan (1948) in a series of replicate counts on the same blood sample, found approximately twice the range that has been found here with 24 different subjects. Because of the small range of normal colour-index figures, there is every reason to hope that small deviations from the normal, which can now be detected reliably, will prove significant indications of disease.

Summary

The colour index has been measured in 24 normal human subjects using an automatic red-cell counter and an M.R.C. photometer. The mean value for the series was 0·99 and the overall coefficient of variation was 4·93%.

I thank Sir Howard Florey, F.R.S., for his continued interest in this work; Dr. R. G. Macfarlane, F.R.S., in whose department most of this work was carried out, and Dr. A. H. Tomlinson for much helpful advice and criticism; and Mr. M. J. Allington, F.I.M.L.T., and other members of the staff of the routine hæmatology laboratory of the Radcliffe Infirmary, who collected the blood samples.

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PARALYTIC BONE LENGTHENING FOLLOWING POLIOMYELITIS

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POLIOMYELITIS in early years is nearly always followed by disturbance of growth of the affected extremity. The extent of this disturbance, and its associations with muscle paralysis, have been described by Stinchfield et al. (1949), Gullickson et al. (1950), and Ring (1957), who have noted the progressive discrepancy which develops between the two limbs in patients with asymmetrical residual paralysis. The attention of most investigators has been directed towards the shortening which occurs as the child grows, and the early growth of the limbs after paralysis has rarely been studied.

In the course of clinical examination of patients who had contracted poliomyelitis some time previously, our attention was drawn to children in whom lengthening of the more paralysed limb apparently developed, and radiographic studies confirmed that this did in fact occasionally occur. Whether this was a normal feature of limb paralysis was more difficult to determine, although Green and Anderson (1955) have suggested that lengthening may occur in the first year. In examining scanograms of 30 children taken during the first two years of paralysis, Lerique (1956) observed that in 12 the affected limb showed lengthening.

This phenomenon of early lengthening is rarely appreciated, partly because it is slight, partly because it is transient, and partly because the patients are often not ambulant. It is rarely of clinical significance, although occasionally raising the shoe of the unaffected leg may be necessary to maintain a level pelvis and a facile mode of walking.

Material and Method

We have confined our observations to children aged 2–12 years under the care of a single physician at Queen Mary's

Hospital for Children, Carshalton. In each case the date of onset (in 1955–57) was known precisely. At an initial survey those with little or no lower limb paralysis, whose stay in hospital might be expected to be very brief, were excluded. It was our intention to examine and radiograph patients during the first month after onset, and thereafter at three-monthly intervals in the first year and at six-monthly intervals in the second year, a final examination being made two years after onset. In fact complete records for the two years could not be obtained, and the conclusions are derived from those patients who were under our observation for six months or more.

At each examination the power of the main muscle-groups of the legs was estimated and charted according to the M.R.C. scale, where 0 represents complete paralysis and 5 represents full muscle power. The muscles were examined in twenty groups and the total muscle power of the limb was expressed as the muscle score, that of the normal limb being 100. In most patients there was detectable weakness of both legs, and subtraction of the muscle score of the weaker leg from that of the stronger was used to give an index of the difference of muscle power between the limbs. The lengths of the legs was measured clinically from the anterior superior spine to the medial malleolus. The mid-thigh circumference and the circumference of each calf was measured, and from these measurements the amount of wasting of both thigh and calf was estimated. A scanogram of the legs was then taken, and the lengths of each femur and tibia were measured upon the dry film. The femur was measured from the top of the head to the intercondylar notch and the tibia from the intercondylar notch of the femur to the upper surface of the talus. These measurements were made by one of us without prior knowledge of the extent of the paralysis.

Observations

Of the 59 patients with a significant residual lower-limb paralysis there were 11 in whom we could detect no difference between the amount of muscle loss, or between the muscle scores; and these patients have been excluded from this series. There were 48 patients with an asymmetrical lower-limb paralysis, but only 2 of these had no detectable involvement of one leg. Whilst it is an advantage to have one normal leg as a standard for comparison, it is our impression that strictly unilateral involvement in the early stages of poliomyelitis is relatively rare.

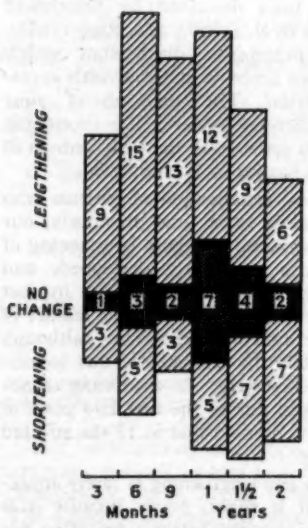

Fig. 1—Histogram indicating numbers of patients with tibial lengthening or shortening in the more paralysed leg at varying periods after the onset of the disease.

Excluding those in whom the limbs were of equal length, and assuming that inequality of leg length is normally distributed at random, then for the first year after onset $\chi^2=11{\cdot}5$, $P=0{\cdot}02$.

There were 113 clinical and X-ray examinations carried out in the 48 patients with asymmetrical paralysis of the limbs. For each of the periods after onset a histogram was constructed showing the number of patients in whom the bones of the legs were equal in length and the numbers showing either shortening or lengthening of the more paralysed limb. The measurements for the femur and tibia were considered separately, and any detectable difference between the bone lengths was considered to be of significance. It is difficult to define the experimental error of the scanogram, but by expressing the results in this way we hoped that errors of technique and measurement would be scattered evenly between the two limbs.

The measurements of the tibia are shown in fig. 1. Three months after onset most of the radiographs showed lengthening of the more paralysed leg, and this change was more distinct in the observations taken at six months and at nine months after onset. At the end of the first year, while many of the tibiæ showed lengthening, a considerable number were shorter and the later observations indicated that shortening became progressively more common. Grouping together the observations for the first year, 49 radiographs showed paralytic lengthening of the tibia, 16 showed shortening, and 13 showed equality.

Observations on the femur for the same period are seen in fig. 2. During the first year 38 radiographs showed paralytic lengthening of this bone, 13 showed shortening, and in 27 the bone lengths were equal. In the femur, as in the tibia, during the second year shortening became the more common phenomenon. In most patients the difference in length between the two bones was slight, and the maximum lengthening of the leg as a whole in this series was 11 mm. comprising 3 mm. in the tibia and 8 mm. in the femur.

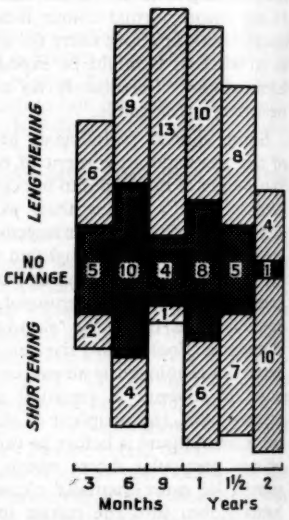

Fig. 2—Histogram indicating, as in Fig. 1, lengthening or shortening of the femur.

For the first year $\chi^2=7{\cdot}65$, $P=0{\cdot}10$

The measurements of the patients with asymmetrical leg paralysis have also been examined, to determine the frequency of overall lengthening of the more paralysed limb. There were 33 patients for whom there were radiographs taken in the first year after onset. Of these, 23 had paralytic lengthening; in 4 cases the legs remained equal in length; and in 6 the legs became progressively shorter. We were unable to separate the first from the third of these groups by simple clinical examination. There was no difference between the pattern of muscle paralysis in the two groups, nor was there any clinical evidence that a vascular factor distinguished one; the paralysed limb which is longer than its fellow may still be cold and show evidence of cutaneous vascular insufficiency.

Discussion

Paralytic lengthening of a limb in the first year after an attack of poliomyelitis occurs in most patients in whom there is a detectable difference between the residual

muscle power of the two legs. It is a temporary phase, which is almost always followed by shortening. Since there is no evidence that the virus of poliomyelitis affects the bone itself, the changes in length must be secondary either to the disturbance of nerve-cells, to the paralysis of muscles, or to changes in the blood-flow of the limb.

Damage to nerve cells in poliomyelitis affects primarily the anterior-horn cells, and the motor fibres from these cells have no direct spread to bone. The main innervation of this tissue is derived from the autonomic nervous system, and fibres pass in along the vascular channels (Hurrell 1937). In growing bone the osteoblasts themselves may receive a nerve-supply (de Castro 1929). Damage to the sympathetic outflow may produce hyperæmia of bone, as Fell (1949) has shown by experiments in the kitten. This hyperæmia may be associated with an increase in the rate of growth (Goetz et al. 1955). The rate of growth may also increase after sympathectomy in the child (Harris and McDonald 1936). There is no clinical evidence that sympathetic paralysis of this type occurs in the early stages of poliomyelitis, although the distribution of the lesions would suggest this as a possible factor.

Since it has been shown that the extent of paralysis is an important factor in the disturbances of bone growth which follow poliomyelitis, it is possible that paralytic lengthening may itself be a mechanical change. Paralysis of muscles is normally followed rapidly by bone atrophy (Abramson 1948), and there is commonly an inverse relationship between the rate of growth of bone in width and in length. In this relationship, however, it is the epiphyseal cartilage that seems to play the dominant role, and it is unlikely that bone atrophy itself could directly influence the rate of growth in length.

As a result of the muscle paralysis, changes in blood-flow in the limb undoubtedly occur and the diminution of metabolic demands by the muscle leaves available for the bone a rather greater proportion of the normal blood-supply. Thus an internal shunt leading to hyperæmia of the long bones may play a part.

Of the possible explanations of paralytic lengthening of bone in the early stages of poliomyelitis, one of the likeliest is that growth in breadth is indirectly associated with growth in length. If we are to regard the action of the epiphyseal cartilage as twofold—(1) to add to the growth in length of bone by endochondral ossification, and (2) to add to the width of the cartilage plate by peripheral accretion—then the depression of the latter activity as a result of muscle paralysis may leave available a considerable growth potential. The resulting increase in length reaches an equilibrium after a year or so as the cartilage responds to its new environment.

Postscript

In describing the lengthening of bones soon after a limb has been paralysed we had the impression that this had only recently been noted. We were therefore somewhat chastened to find that Ollier in 1867 also remarked on the same phenomenon:

"Le léger degré d'allongement du membre que nous signalons ici n'est pas constant, probablement parce que les troubles de nutrition commencent immédiatement; mais nous l'avons observé une fois chez l'homme et très fréquement chez les animaux sur lesquels nous avons expérimenté et dont nous citerons bientôt les observations. On constate, dans ces cas-là, une plus grande longueur de l'os, mais un arrêt de développement en épaisseur; l'os s'est allongé en restant plus mince. C'est ce que nous désignerons sous le nom d'*allongement atrophique*."

Summary

The growth of the lower limbs in the first two years after an attack of poliomyelitis has been studied in 48 children with an asymmetrical lower-limb paralysis.

In the first year after the onset of the disease, of 33 patients observed, 23 showed overall lengthening of the more paralysed limb. 6 patients showed progressive shortening of the limb from the onset of the disease.

There appeared to be no clinical distinction between these two main groups.

In the second year after onset the more paralysed limb was usually the shorter.

We are greatly indebted to Dr. David Lawson for permission to examine and report on patients under his care; and to Miss M. M. C. Reardon, Miss B. Laye, and Miss Stella Poole for their assistance in the organisation of this study. This work was assisted by a grant from the National Fund for Poliomyelitis Research.

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CHLORPROPAMIDE

A NEW HYPOGLYCÆMIC AGENT

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CARBUTAMIDE and tolbutamide have been shown to control diabetes in certain patients who would otherwise require insulin. Carbutamide has been regarded by some (Kirtley 1957, Duncan and Baird 1957, Phemister 1957) as too toxic, and tolbutamide, which appears to produce fewer side-effects, has largely supplanted it. Tolbutamide, however, is less potent, and because its hypoglycæmic action is of shorter duration it often has to be given thrice daily. We report here results obtained in 43 cases with a new preparation, chlorpropamide [N-propyl-N-(*p*-chlorobenzene sulphonyl)urea].

The patients selected for this trial were essentially of the type described by Bertram et al. (1955) as most suitable for oral therapy: they were less than ten years' diabetic, were over 40 years old, and had taken insulin, if at all, for not more than two years. Only 2 patients were obese, although 17 others had been so. Diet alone had not sufficiently controlled the diabetes.

As in our original investigation of carbutamide (Murray and Wang 1956), the dose of chlorpropamide was 1 g. daily at breakfast, but no "loading" dose was given in the first two days' treatment. 13 patients were in hospital and 30 were not. The outpatients kept records of urine tests (using 'Clinitest') before each of the three main meals of the day. This method proved reliable, corresponding well with the results of determining glucose output in twenty-four-hour collections of urine (Murray and Wang 1958). These collections were obtained in most cases on two consecutive days before starting the drug, and again on two days towards the end of a fortnight's treat-

SUMMARY OF CASES

Patients	Response to chlorpropamide	
	Success	Failure
Number treated	28 (8M, 20F)	15 (3M, 12F)
Over 40 at onset of diabetes	27 (96%)	15 (100%)
Previously obese	11 (39%)	8 (53%)
Duration of diabetes:		
"New cases" (<3 months)	4	5
<10 years (excluding "new cases")	17	10
>10 years	7	0
Previously taking insulin:		
For 2 years or less:		
Dose <21 units	1	2
Dose >20 units	1	0
For more than 2 years:		
Dose <21 units	7	2
Dose >20 units	3	1
Total	12 (43%)	5 (33%)
Previous history of ketonuria	1 (4%)	4 (27%)

ment. At each attendance at the clinic, in the forenoon, the blood-sugar was estimated. For the inpatients similar but more frequent observations were made.

A satisfactory response to 1 g. chlorpropamide daily was obtained in 28 of the 43 patients treated. As the table shows, the two groups of patients—successes and failures—were similar except that ketonuria had previously been noted in 4 (27%) of the failures compared with only 1 (4%) of the successes. In the successes a satisfactory response was evident generally by the second or third day, and always within seven days (mean 3·2 days), all three daily urine tests being recorded as "blue" or at worst showing an occasional "trace" (¼%). In the successful group the mean blood-sugar level fell from 273·5 mg. per 100 ml. before treatment to 161·8 mg. at the end of two weeks, while in the unsuccessful the comparable values were 364·9 mg. and 304·5 mg. In these successful cases in which the urinary glucose output was determined as described above, the mean daily output was reduced from 35·5 g. to 3·4 g. daily, whereas the mean figures for unsuccessful cases were 58·3 g. per day before chlorpropamide was given, and 59·6 g. at the end of the course. Since the mean blood-sugar value and the mean urinary glucose output were higher, before treatment, in the group which failed to respond, it might be supposed that this group were more severely diabetic; but no such difference was apparent clinically. For example, one woman who made a rapid and excellent response to the drug had acute symptoms, ketonuria, and a blood-sugar level of 420 mg. per 100 ml. before treatment was started.

Some of the patients had previously received carbutamide or tolbutamide. Of the 28 cases responding satisfactorily to chlorpropamide, 3 had had carbutamide, 4 had had tolbutamide, and 8 had been tried with both. Carbutamide 1 g. daily had proved effective in all, while tolbutamide had given satisfactory results in 9 at a dose of 0·5 g. three times daily, but had failed in 3, even at double this dose. Among the failures with chlorpropamide 6 had been treated with the other sulphonylureas: all had failed with tolbutamide but 3 had responded to carbutamide. The impression gained from these few observations is that chlorpropamide is somewhat less potent than carbutamide, but definitely more potent than tolbutamide.

In 5 patients who did not respond well to 1 g. the dose of chlorpropamide was increased, 4 receiving 2 g. daily, and the other 3 g. In 3 cases this increased dosage brought satisfactory control. Nevertheless these cases have been regarded as "failures", since, for reasons given below, we think it undesirable to exceed 1 g. daily.

Though there were no serious toxic effects, and never any evidence of either leucopenia or thrombocytopenia, 9 patients showed side-effects—in 4 cases after the dose had been increased to 2 g. The untoward effects were nausea (insufficient to call for abandonment of treatment) in 7 cases, a diffuse erythematous rash in 1, and drowsiness (unaccompanied by hypoglycæmia) in 1. Because of this evidence of toxicity, occurring particularly on higher dosage, we concluded that the dose of chlorpropamide should not exceed 1 g. daily, and we are now trying smaller doses. Satisfactory results have already been obtained with 0·5 g., but further experience is required before deciding on the best dosage. Provisionally we would advise commencing treatment with 1 g. daily, taken as a single dose, and reducing this as soon as a good response is obtained. In suitable cases this method seems likely to control diabetes while avoiding undesirable side-effects.

Conclusions

Chlorpropamide is an effective oral hypoglycæmic agent in the treatment of diabetes, although its action, like that of similar drugs, is somewhat unpredictable.

In most cases which respond, a single daily dose of 1 gramme is sufficient, and this amount should not be exceeded. If after a few days' treatment, a good response is obtained with 1 g. daily, the dose should be reduced—to the lowest level found effective.

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RETENTION OF SODIUM DURING UNDERNUTRITION

WITH A NOTE ON THE RELATION OF THE EXTRACELLULAR SPACE TO GROWTH AND AGEING

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A RETENTION of water has often been described in undernutrition, and the reasons for it have been much discussed (Sinclair 1948, Keys et al. 1950, McCance 1951, Helweg-Larsen et al. 1952). On one point all are agreed—namely, that the excess water is retained in the extracellular space. It is, however, still a question at issue whether there is an absolute increase in the amount of extracellular fluid (E.C.F.) or whether, there being no change in the absolute amount of E.C.F., there is a relative increase because the cells have shrunken. Precise interpretation of some workers' results is difficult because they have studied hunger œdema, but the problem of hunger œdema is not necessarily germane to that of simple undernutrition, since it may well represent a distinct pathological process. Hunger œdema may affect the

TABLE I—AGES, HEIGHTS, AND INITIAL WEIGHTS OF THE EXPERIMENTAL SUBJECTS

Subject no.	Sex	Age (yr.)	Height (cm.)	Weight	
				kg.	% of "standard weight" *
1	M	38	183	90	113
2	M	38	173	97	136
3	F	46	165	82	123

* The standard weight was calculated from the tables of the Association of Life Insurance Directors and Actuarial Society of America, New York, 1912 (Sunderman and Boerner 1949).

serous cavities (Prym 1921) and is not related to the degree of wasting (Brozek et al. 1946, Helweg-Larsen et al. 1952).

von Uehlinger (1947) suggested that during undernutrition the volume of the E.C.F. increased to take up the space left by the loss of fat and protein tissue, and this suggestion was further developed by McCance (1951). The concept is easy to grasp in the case of the lobster, with a rigid shell and therefore a fixed volume to its body (Morgulis 1916). The same idea can without difficulty be extended to the spaces inside the bones of higher animals (Roger and Josué 1900). But, on the other hand, in these animals the elastic skin and soft connective tissues underlying it clearly must permit changes in the volume

TABLE II—COMPOSITION OF THE EXPERIMENTAL DIETS

Subject no.	Cals.	N (g.)	P (mg.)	K (mEq.)	Na (mEq.)
1	500	4·55	390	31·2	104
2	800	6.89	604	31·2	107
3	500	4·4	421	29·5	106

The calorie contents were calculated from McCance and Widdowson (1946). The chemical composition was determined by analysis.

of their bodies; in fact when muscle atrophies while a limb is inside a plaster cast fluid does not take its place: the limb shrinks.

We have made an experimental study of the gains and losses of the mineral constituents of the body-fluids during a period of undernutrition. The results indicate that, although the E.C.F. does account for a larger than normal proportion of the weight of the body in simple undernutrition, this represents a retention of what was already there rather than a gain of E.C.F. These findings may, we think, be explained very simply by the anatomy of the spaces which the fluid between the cells occupies. The same explanation can be extended to cover the alterations in the amount of water in the tissues during growth and ageing.

Material and Procedure

Three volunteers were studied. Subjects 1 and 2 were male colleagues; they carried on with their normal duties during the experiments. Subject 3 was a woman with osteo-arthritis of the hips; she was up during the whole of the day but was not very active. All were overweight (table I). They were weighed daily under standard conditions. Their experimental diets provided 500 or 800 calories, of which about a quarter was derived from protein and the remainder largely from carbohydrates (table II). Each of the experimental diets was exactly the same every day, but for one week in each experiment potassium citrate (90 mEq. daily) was added. Urine was collected daily and fæces in periods of seven or eight days, and the body's gains and losses of N, P, K, and Na were measured. (The results of the balances of Cl had to be rejected because, through an oversight, the diets for analysis had been preserved with chloroform.) Insensible losses were not measured. Blood was taken, usually twice in each period, for the determination of the packed-cell volume (P.C.V.), plasma-proteins, and electrolytes. The methods have been described elsewhere (Fourman 1953).

TABLE III—THE LOSSES OF WEIGHT AND THE GAINS (+) AND LOSSES (—) OF DIFFERENT ELEMENTS WITH THE EXPERIMENTAL DIETS

Subject no.	Duration of experiment (days)	Loss of weight (kg.)	Balances			
			N (g.)	P (g.)	K (mEq.)	Na (mEq.)
1	24	8·9	− 74·8	−7·52	−100	+153
2	42	12·9	−101·2	−8·89	−385	+287
3	24	5·9	−36·6	−5·33	−147	+36

Results

The clinical and metabolic effects of the diets we used are well known (Evans 1942, Rynearson and Gastineau 1949, Strong et al. 1958). The subjects felt well during the experiments and did not become ketotic.

TABLE IV—CALCULATED LOSSES OF PROTEIN TISSUE AND OF FAT

Subject no.	Total weight loss (kg.)	Protein loss (kg.)	Fat loss (kg.) (by difference)
1	8·9	2·2	6·7
2	12·9	3·0	9·9
3	5·9	1·1	4·8

Table III shows the losses of weight and also the amounts of N, P, K, and Na the subjects had lost or gained at the end of their period of undernutrition. As was to be expected (Quinn et al. 1954), all three subjects incurred a loss of the constituents of protein tissue, N, P, and K. There was an apparent gain of Na of 6·3 mEq. per day in subject 1, 7 mEq. per day in subject 2, and 1·5 mEq. per day in subject 3; the insensible losses account for these amounts (Freyberg and Grant 1937, Newburgh and Leaf 1950). The trend of the balances was not altered by the administration of potassium citrate (compare Duncan et al. 1948). The values for the P.C.V. and the other constituents measured in the blood did not change, and there was no evidence of hæmodilution.

Discussion

From the analytical results it is possible roughly to apportion the changes in weight to different constituents of the body. The balance of Na showed no significant change. This indicates there was no change in the total volume of the E.C.F.

TABLE V—CALCULATED DAILY EXPENDITURE OF CALORIES

Subject no.	from protein	from fat	from diet	Total
1	81	2300	500	2880
2	63	1890	800	2690
3	40	1600	500	2100

The losses of nitrogen were accompanied by losses of K and P. It may be assumed that the loss of nitrogen represented a loss of protein tissue and not of connective tissue, for the direct analysis of rats has shown that the nitrogen lost in starvation is derived from muscle cells and not stroma (Hagan and Scow 1957).

Losses of K and P on the other hand do not depend solely on losses of protein tissue (Fenn 1939, Homburger et al. 1952), and their relation to the losses of nitrogen in our experiments was quite variable. We have based our calculation of the amount of protein lost on the losses of nitrogen. In muscle 1 g. of N corresponds to 30 g. of tissue (Reifenstein et al. 1945), and on this basis the losses of N corresponded to 2·2, 3·0, and 1·1 kg. of tissue in subjects 1, 2, and 3 respectively. The remaining loss of weight was presumably accounted for by a loss of fat (table IV).

In spite of the large contribution of protein tissue to the loss of weight in these subjects, it represented but

a small gain of calories to their economy (table v). The calculated loss of fat contributed largely to the total output of calories. The calculated figure for the total calorie output corresponds well with the expected calorie outputs for these subjects, and supports the interpretation placed on the results.

This may be stated as a loss of cell substance and therefore of intracellular fluid—the cells shrink. The total volume of E.C.F. does not change; therefore the E.C.F. must form a higher proportion of the total body water. This interpretation agrees with the results of Moore et al. 1956, and of McConkey (unpublished), obtained by measuring the E.C.F. and the total water of the body by the dilution principle in wasted and normal people.

A consideration of the spatial arrangement of the E.C.F. explains why this must be so. The E.C.F. consists of the fluid of the plasma, the lymph, and the tissue spaces, the tissue spaces accounting for about half the whole. Now the fluid of the tissue spaces is distributed as a thin film on the surface of cells, and in connective tissue (Manery 1954). Connective tissue itself is a watery gel. In undernutrition the fat cells of course shrink (Jackson 1925), but there is no change in their total number. The muscle cells also atrophy (Jewesbury and Topley 1913, Moulton 1920, Jackson 1925, Adams et al. 1953). But all these cells must retain their surrounding film of water; and the volume of the connective tissue probably remains unchanged (Bramwell and Muir 1907, Adams et al. 1953, Waterlow and Mendes 1957). Hence, as can be demonstrated by direct analysis, the water content of fat (Sedlmair 1899, Bozenraad 1911) and of muscle increases (von Voit 1866, Mendel and Rose 1912, Waterlow and Mendes 1957). The volume of the blood does not decrease (Perera 1946, Henschel et al. 1947, Mollison 1946, Walters et al. 1947, Sunderman 1947); and it is probable that the volume of lymph, which is at least as great as that of plasma (Abel et al. 1938), also remains the same. It is clear, then, that in undernutrition the proportion of E.C.F. in the body must increase, though the absolute amount need not. In simple undernutrition, we consider that a *relative* increase in the volume of the E.C.F. is a geometrical necessity if each cell is to retain intact its watery environment. It is unnecessary to imagine that spaces left by fat have to be filled to preserve "tissue tension".

It may be noted that the variations in E.C.F. with age can also be interpreted on the basis of the geometrical changes in various tissues. In infants the proportion of E.C.F. is higher than in adults (Forbes et al. 1956, Friis-Hansen 1957); this is largely because their muscles contain a larger proportion of water (McCance and Widdowson 1956). The muscle fibres, and the cells making them up, are smaller than in an adult, and have a larger surface area in relation to their total bulk.

After the sixteenth week of embryonic life in the human the growth of muscle is by hypertrophy, and not by hyperplasia, and the total number of fibres and of cells probably does not increase (Adams et al. 1953); hence in the grown muscle the surface area of the cells is smaller in proportion to the total bulk than in infants and the amount of fluid required to bathe them is smaller in relation to the total volume of the tissue. Liver on the other hand grows by hyperplasia and the size of the cells does not change appreciably. It is not surprising, then, that the composition of the liver does not vary greatly with age (Nishimura and Inakake 1957).

Finally, on the basis of our interpretation, one would expect the proportion of E.C.F. to increase in muscle when it atrophies. It does (Eichelberger et al. 1958). And in old age, when the fibres shrink, the water content of muscle increases (Ranke 1865).

Summary

In three moderately obese people the effects of simple undernutrition were studied, in two of them for three weeks, in one for six weeks.

They lost protein tissue and fat but they did not gain sodium. There was no evidence of an increase in the absolute amount of the extracellular fluid (E.C.F.), though the proportion of E.C.F. in their bodies increased.

It is suggested that a relative increase in the volume of the E.C.F. must inevitably accompany wasting, if the cells which shrink are to retain their normal covering film of fluid. This concept has been extended to explain the changes in the volume of the E.C.F. which accompany growth and atrophy.

This paper was written as a result of a lively discussion at a Ciba Foundation Colloquium (see Colloquia on Ageing, vol. 4: Water and Electrolyte Metabolism in relation to Age and Sex; pp. 113, 162. London, 1958).

A large part of the work for the experiments was done in Oxford in 1952, and we wish to express our indebtedness to Prof. L. J. Witts and our colleagues there. We are grateful to Prof. Harold Scarborough for his advice and encouragement. One of us (B. McC.) received a grant from the endowment fund of the United Cardiff Hospitals.

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EXPERIMENTAL NUTRITIONAL SIDEROSIS

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ON the high incidence of severe siderosis in Africans there are now two schools of thought. The first maintains that iron overload *alone* is the cause of this type of siderosis. Its views are summarised by Higginson (1957):

"The significance of diet in Bantu siderosis has yet to be established. It cannot be stated that . . . dietary pattern (apart from excessive iron intake) is a major factor in African siderosis . . . in this region."

On several occasions Higginson's coworkers have insisted that siderosis in Africans can be explained purely by excessive intake of iron in the food and that "no lesion of the digestive tract or any other organ need be invoked . . ." (Walker and Arvidsson 1953).

The second school of thought, initiated by Gillman and Gillman (1945, 1951), attributes this type of siderosis primarily to an intracellular metabolic disorder, probably started by chronic malnutrition—even though the excessive bodily iron comes, of course, from the food. Kinney, Hegsted, and Finch (1949) demonstrated that, in rats, at least, uptake of iron from an iron-rich diet varies with other components of the diet.

Higginson (1957) wrote:

"In rats fed a diet of maize porridge and sour milk supplemented by iron, I was unable to demonstrate increased iron deposition as compared to a control group on a stock diet."

This was so strongly at variance with other reports (Kinney et al. 1949, Finch et al. 1950, Rather 1956) that we thought it essential to reinvestigate the relation of a bad diet to dietary siderosis.

Experiment and Results

Adult male rats were fed either our stock ration or uncooked mealie meal; 4% ferric citrate was added to the food of half the rats on each diet. These diets were fed ad libitum and fresh milk was also made freely available. Liver biopsies were done on several rats in each group at 50 or 100 days, and the experiment ended at 156 days. The iron contents of the diets, and also of the livers, spleens, kidneys, pancreases, blood, and entire carcasses of the rats, were determined, while iron distribution was studied histochemically in sections of the above and of several other tissues.

The iron content of the whole body, and of the livers and spleens, of the groups of rats receiving the different diets is shown in the table. The distribution of iron in the livers of experimental and control rats, at different stages of the experiment, is illustrated in figs. 1–3.

Our observations may be summarised as follows:

1. The total body-iron was greater in rats on a mealie-meal diet than in rats on a good stock ration. The hepatic and splenic iron were not significantly different.

2. The iron uptake both from mealie-meal and from stock diets was considerably increased when iron was added to them.

3. The total body-iron of rats on the iron-enriched mealie-meal diet was more than double that of rats on the iron-enriched stock diet. Moreover, the hepatic iron in the former group was almost six times that in the latter. On the other hand, the splenic iron in rats fed mealie meal plus iron was not quite twice that of rats fed the stock diet plus iron. The table also shows that the contribution of hepatic iron to the total body-iron varied from 6 to 12% in all groups except the rats fed mealie meal plus iron. In the latter, hepatic iron constituted 37% of the total body-iron, clearly indicating the predilection of the liver to siderosis, in this dietary setting. The histochemical data fully substantiated these chemical findings.

CONCENTRATION OF IRON IN LIVER, SPLEEN, AND TOTAL BODY

Diet	No. of rats	Daily intake •		Concentration of iron (mg. per 100 mg. wet weight) in			Ratio of total liver-iron to total body-iron
		Food (g.)	Iron† (mg.)	Total body ‡	Liver	Spleen	
Stock	5	23	18	8·2±0·5 §	32·3±2·5	115±15·4	0·12±0·01
Stock + iron citrate	10	20	203	18·5±1·0	66·6±6·3	405±35·2	0·12±0·01
Mealie meal	5	13	0·6	12·3±0·6	22·1±2·4	114±10·3	0·06±0·02
Mealie meal + iron citrate ‖	7	11	107	45·1±2·2	367±19	765±50	0·37±0·03

• Mean daily intake per rat.
† Iron in diet and milk.
‡ Iron content of perfused carcass + estimates for tissues removed for histology and chemical analysis, and for iron in plasma and hæmoglobin.
§ Standard error of the mean.
‖ Note greater concentrations of tissue iron despite lower daily iron intake, as compared with group on stock diet + iron citrate.

4. Another notable finding, not hitherto reported in experimental siderosis in rats, was that in the milder (earlier) degree

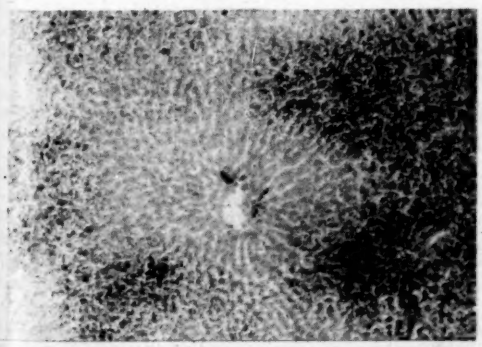

Fig. 1—Liver of rat after 50 days on mealie-meal diet enriched with iron; siderosis (dark staining) of liver cells especially around portal tracts. Only a few Kupffer cells near the central vein contain iron. (× 76.)

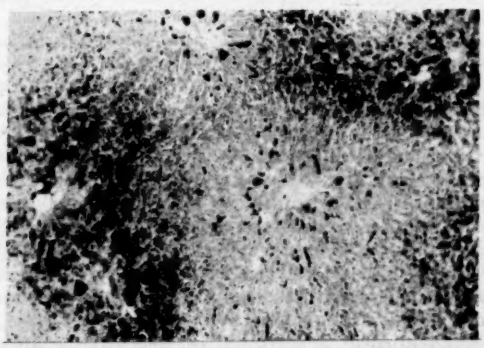

Fig. 2—Liver of rat after 156 days on mealie-meal diet enriched with iron. Massive siderosis with clumping of iron-containing granules in liver cells in portal half of each lobule. Siderosis and clumping of siderin in sinusoidal and portal phagocytes is well marked. (× 76.)

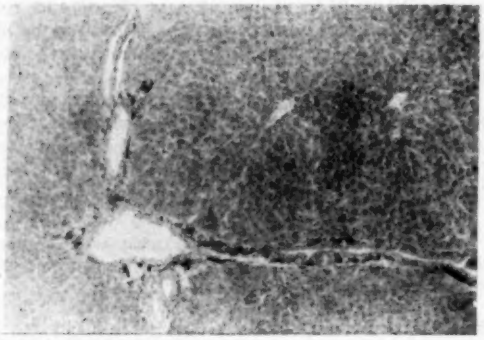

Fig. 3—Liver of control rat fed good stock diet plus ferric citrate for 156 days. Siderosis absent, only small amounts of iron being detectable in a few sinusoidal and portal phagocytes. (× 76.)

of siderosis the excess iron within the liver was at first confined to the liver cells themselves. Only later, when the hepatocellular iron granules became very numerous, large, and clumped, did sinusoidal and portal phagocytes become laden with iron—possibly through ingestion of effete iron-laden liver cells. This finding, in rats, exactly conforms with that noted first by Gillman and Gillman (1945, 1951) and later by Wainwright (1957) and by us (Gillman 1957, Gillman, Hathorn, and Lamont 1957, Gillman, Lamont, Hathorn, and Canham 1957), in the early stages of African siderosis.

Comment

Thus, not only did the (defective) mealie-meal diet promote significant increases in the uptake of iron (especially from an iron-enriched diet), but this iron was usually detected, initially, within the liver cells. It therefore seems that—as in the African, so too in rats—only when hepatic siderosis is gross may large amounts of iron be found in hepatic reticuloendothelial cells or in the epithelial and parenchymal cells of other organs—apart from spleen, bone-marrow, lymph-nodes, and intestinal mucosa.

It remains to be determined whether the excessive iron uptake of rats on a bad diet is a function only of the associated unfavourable ratios of iron, calcium, or phosphate. Iron uptake is known to be affected by dietary phosphate (Hegsted et al. 1949) and dietary calcium (McCollum et al. 1939, Chapman and Campbell 1957). The role of other dietary components such as phytate and protein (Rather 1956) also merits further study.

We also want, once again, to focus attention on disturbances in intracellular metabolism as a possible basis for excessive iron uptake. It has been shown for humans (Gillman, Mandelstam, and Gillman 1945, Gillman and Gillman 1951), and now (in the present study) for rats, that iron absorbed in excess from the food is initially deposited within the liver cells themselves, and not in the reticuloendothelial system. In the African such hepatocellular iron deposition was shown by Gillman and Gillman (1944) to occur first in relation to mitochrondria which are now generally accepted as important foci of cell metabolism. These observations are now supported by Richter's electron-microscope studies indicating that hepatocellular iron is derived from altered mitochondria or " siderosomes " (Richter 1957).

Of particular importance, in this regard, are the findings that anoxia—induced by hæmorrhage (Bothwell and Finch 1957) or decompression (Smith et al. 1957, Colehour et al. 1957)—increases the uptake of dietary iron, and the iron content and total iron-binding capacity of the serum. The increased iron-binding capacity, so striking a phenomenon in siderotic Africans (Gillman, Lamont, Hathorn, and Canham 1957), may perhaps be one expression of seasonal nutritionally induced metabolic anoxia. Moreover, these effects of anoxia are much greater in older rats than in young ones (Garcia 1957). This last finding may have as its clinical counterpart the fact that definite siderosis has not yet been observed in Africans under the age of about 14.

Because of these findings, and the frequency of anoxic changes in hepatic cells in malnourished adult and infant Africans (Gillman and Gillman 1949, 1951) as well as in our experimental rats, we are now investigating the possibility that some form of cellular anoxia, induced perhaps by chronic malnutrition, may promote the prolonged excessive iron uptake, with consequent severe siderosis, so commonly found among Africans in the Union. Our preliminary findings indicate that intermittent decompression ($1^1/_2$ hours twice weekly at about 360 mm. Hg) promoted rapid and marked increases in hepatic iron, especially in rats fed the mealie meal but not the stock diet—both iron-enriched. A similar but less marked trend was also noted when the calcium and phosphate contents of the two diets were equalised. These findings are in line with recent evidence of the importance of intracellular iron-containing enzymes even in " iron-deficiency " states. Beutler (1957) demonstrated a fall in the concentration of several of these enzymes in liver and kidney, long before anæmia was notable; he implied that the symptoms of anæmia may not be attributable solely to the decrease in oxygen-carrying powers of the blood, resulting from the low hæmoglobin, but rather to preceding and persistent derangement in intracellular iron enzymes and consequent impairment in cellular oxidation processes. Even the hepatocellular iron deposits described in megaloblastic anæmias may, as suggested by Gillman and Gillman (1951, p. 343) be the result of intracellular enzymic changes.

Conclusion

Our present results support those of several other similar experiments in the literature showing that dietary iron overload *alone* does not readily induce severe parenchymal cell siderosis if the basal diet is good. Also, a bad diet rich in iron produces much more severe siderosis than one low in iron.

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ULCER UNDER THE RIBS

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IF, after a partial gastrectomy or gastrojejunal anastomosis for a peptic ulcer, the patient is unfortunate enough to develop an anastomotic ulcer, it may cause pain just above or just below the left costal margin. This may lead to difficulty in diagnosis.

Case-reports

Case 1.—In January, 1957, a man aged 60 was referred to the thoracic department of the Bradford Royal Infirmary with recurrent peptic ulceration.

He had a duodenal perforation sutured in 1951, a partial gastrectomy in 1952, and a higher gastrectomy with Roux-en-Y reconstruction for stomal ulcer in 1955. In 1956 he developed a gastrojejunocolic fistula; and the colon and stoma were freed and each closed separately. Vagotomy was attempted but abandoned. After some improvement he began to deteriorate and to lose weight.

The most striking feature of the history was severe attacks of intermittent pain. These were localised to the left costal margin, to the præcordium, and occasionally to the left shoulder, the left arm, and the left side of the neck. The pain was so severe that he required regular doses of pethidine. A barium meal in February, 1957, showed a deep ulcer penetrating the diaphragm.

The patient was explored through a thoracoabdominal incision. The tissues beneath the diaphragm were very œdematous; and, on separating the stomach remnant, an ulcer 5 cm. in diameter was found penetrating the diaphragm and involving the chest wall. The ulcer had also penetrated the spleen; and it was adherent to the transverse colon and to the jejunal loop. The stomach remnant and the spleen were removed and the jejunal loop was brought up behind the transverse colon and anastomosed to the œsophagus.

Postoperative recovery was satisfactory; and six months later the patient was free from pain.

Case 2.—A man aged 63 was transferred to the thoracic department of the Leeds General Infirmary in September, 1956.

In 1951 he had undergone a partial gastrectomy with antecolic gastrojejunostomy for a longstanding duodenal ulcer. After eighteen months he developed an anastomotic ulcer which was treated medically for two years. A laparotomy was then done with a view to higher partial gastrectomy; but, because of dense adhesions to the undersurface of the diaphragm, this was abandoned. A transthoracic vagotomy was performed instead.

A few months later the pain returned: it was severe and situated in the left hypochondrium and above the left costal margin. It was not relieved by food or by antacids. A barium meal showed a huge anastomotic ulcer crater.

On exploration through a left thoracoabdominal incision the omentum was seen to be adherent to the costal margin of the left diaphragm. On attempting to dissect off the stomach and the anastomosis from the diaphragm a large ulcer crater was opened. It measured 5 × 4 cm.; and it was 2 cm. deep. Its base involved the 6th and 7th costal cartilages and the intervening intercostal bundle. A total gastrectomy was performed, together with excision of the stoma and jejunum to beyond the ulcer. A Roux loop was fashioned to restore intestinal continuity. Convalescence was satisfactory, and a year later the patient was free from pain and gaining weight.

Case 3.—A man aged 49 had a partial gastrectomy in 1951 for an old duodenal ulcer. Seven months later he began to complain of epigastric pain after meals. It was situated in the left hypochondrium; and it was not relieved by food or alkalis. Repeated radiological investigations were negative until June, 1954; a probable anastomotic ulcer was then demonstrated.

At *laparatomy* a stalk of fibrous tissue, 1 cm. thick, was found, connecting the jejunum distal to the anastomosis to the anterior abdominal wall just below the costal margin. The stalk was divided, and, after dismantling the anastomosis, the jejunum containing the ulcer was excised, and an end-to-end anastomosis was carried out. A higher partial gastrectomy and vagotomy were then performed.

Postoperative recovery was satisfactory. The man is free from pain and enjoying good health four years later.

Case 4.—A man aged 49 had a Bancroft partial gastrectomy in December, 1952, for a duodenal ulcer of fifteen years duration. On the seventh postoperative day he complained of stabbing pain under the left costal margin, worse on movement; it was relieved for a time by food or drink but there was severe hyperæsthesia over the affected part. Treatment with local anæsthesia brought no improvement. A barium meal was reported as normal.

Six months later the patient was still complaining of pain under the left costal margin, particularly when his stomach was empty; and, by January, 1954, antacids had lost their effect. A barium meal at that time suggested a jejunal diverticulum: only two months later did it show an ulcer crater. This appeared to extend from the region of the anastomosis forwards towards the parietes.

In May, 1954, a large jejunal ulcer was found at operation, 5 cm. proximal to the stoma. It had perforated the diaphragm to involve the chest wall. The jejunum containing the ulcer was excised, leaving the base of the ulcer behind: and an end-to-end anastomosis was performed. A further partial gastrectomy and vagotomy were then done.

The postoperative course was uneventful, and the patient is well and free from pain four years later.

Case 5.—A woman aged 48 had a cholecystectomy and a posterior gastrojejunostomy for a duodenal ulcer in 1954. In January, 1956, she began to complain of periodic pain in the epigastrium, often related to food. A barium meal showed an anastomotic ulcer; and, at operation, a large ulcer was found in the efferent loop. A partial gastrectomy with an antecolic gastrojejunostomy and a lesser-curve valve was carried out. A week later she complained of pain in the left hypochondrium and under the left costal margin, and four days later she had a hæmatemesis of 20 oz. A barium meal before discharge raised the suspicion of an anastomotic ulcer.

Despite strict medical treatment the patient complained of intermittent pain under the left costal margin, in the left chest posteriorly, and in the left shoulder. The pain gradually became more persistent: it was aggravated by deep breathing and heat; and it was not affected by food. In October, 1956, a barium meal showed a large penetrating anastomotic ulcer extending forwards.

A further operation was performed through a left thoracoabdominal incision. On opening the diaphragm an ulcer 3·5 cm. in diameter was found in the anterior wall of the jejunum, opposite the anastomosis; it penetrated the diaphragm at its attachment to the costal margin. The ulcer was dissected off the diaphragm, leaving the ulcer base behind on the chest-wall: the ulcer-bearing segment of the jejunum was then removed, and a subtotal gastrectomy and vagotomy were carried out.

The postoperative course was uneventful, and the patient was free from pain a year later.

Discussion

Adequate partial gastrectomy results in a small gastric stump, the line of anastomosis usually lying deep to the diaphragm. In such circumstances recurrent anastomotic ulceration may involve the diaphragm or occasionally the parietes just below the left costal margin. In the latter event the pain becomes parietal and loses its usual relationship to eating. The patient, moreover, becomes so concerned about the pain under the ribs that he tends to minimise or forget his indigestion.

When the ulcer is so low that it involves the anterior abdominal wall—as used to happen when antecolic

gastroenterostomies were commonly performed—there should be little difficulty in diagnosis. If, however, the ulcer involves the left costal margin, either just above or just below the diaphragm, the symptoms become more difficult to interpret. Pain is then referred to the left shoulder and to the back; and it is influenced by coughing, sneezing, and movement rather than by food or antacids. The pain waxes and wanes as in an ordinary peptic ulcer; but some of the exacerbations are extremely severe. Two of the patients needed opiates to relieve it. If its cause remains undiagnosed the patients may become so disturbed as to develop bizarre symptoms: thus in three of the cases neurosis was seriously considered in the differential diagnosis.

In cases 4 and 5 the pain under the left costal margin appeared in the early postoperative period; it is debatable whether it was a symptom of an extremely early anastomotic ulcer or of a small leak. Illingworth (1953) mentions the occurrence of anastomotic ulcers a few days after operation; but a small leak with local abscess-formation and subsequent fibrosis could simulate it.

Summary

After an adequate partial gastrectomy the anastomosis lies deep to the left diaphragm, and an anastomotic ulcer may penetrate the diaphragm and involve the chest wall.

Five cases are presented: they illustrate that such ulcers are liable to cause severe parietal pain in the region of the left costal margin.

The diagnosis may have to be made despite this misleading localisation and often without abnormal radiological findings.

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LIVER BIOPSY

EXPERIENCES WITH A NEW NEEDLE

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WE have recently used a liver-biopsy needle described by Menghini (1957). This preliminary communication is based on our experience of 83 biopsies.

Needle

The needle, 7 cm. long, is made in diameters of 1 mm., 1·5 mm., and 2 mm. (fig. 1).

The profile of the tip is original: it has an angle of 45° at its end, and is anteriorly convex. This facilitates the cutting and aspiration of the biopsy tissue.

The conventional stylet or trocar is replaced by a blocking-pin towards the head of the needle; this is 2 cm. long and 0·2 mm. smaller in cross-section than the internal lumen of the needle. The blocking-pin allows the passage of fluid to and fro but prevents the aspiration of liver tissue into the syringe and hence minimises fragmentation of the biopsy material.

Technique

The technique is biopsy by aspiration. The patient either lies supine in bed with the right side near the edge, or half-inclined on the left side. The intercostal route in the mid-axillary or anterior axillary line in the right 8th or 9th intercostal space is preferred. After local infiltration with 2% procaine a nick may be made in the skin with a scalpel. The biopsy needle is attached to a record syringe which contains about 2 ml. of normal saline. First the needle is thrust into the subcutaneous tissue to an appropriate depth prefixed by an adjustable guard; and 1 ml. normal saline is injected to free the needle of any subcutaneous tissue which might block its tip.

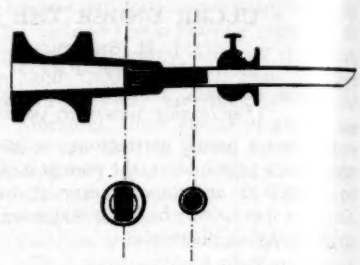

Fig. 1—Liver-biopsy needle.

The guard is now moved backwards 3·5–4 cm. from the tip. The patient holds his breath in expiration; and with constant suction at the syringe, the needle is advanced quickly into the liver. It is then rapidly withdrawn.

The remaining 1 ml. of normal saline in the syringe helps to deliver the cylinder of liver tissue thus obtained into a container. The puncture wound in the skin is sealed with collodion. With the right elbow resting against the biopsy site to apply hæmostasis, the patient now lies on the right side for thirty minutes.

Outpatients, who were admitted for biopsy in the morning, were fit for discharge the same evening.

Liver biopsy was done where liver dysfunction needed confirmation, in unexplained hepatomegaly with normal liver-function tests, and in suspected miliary granulomatous conditions or amyloidosis. The biopsy material varied from 0·5 × 0·1 cm. to 4 × 0·1 cm. in size: it usually included a fair sample of liver tissue (fig. 2). On 5 occasions the tissue was fragmented. In 25 cases no portal tracts were included in the sections.

The biopsy provided a definite diagnosis in 23 cases: fatty change, and other non-specific changes were seen in 42; and normal liver tissue was obtained in 18.

In a review of 20,016 hepatic biopsies from the literature Zamcheck and Sidman (1953) reported an incidence of 0·28% of major complications. Of these hæmorrhage was the most

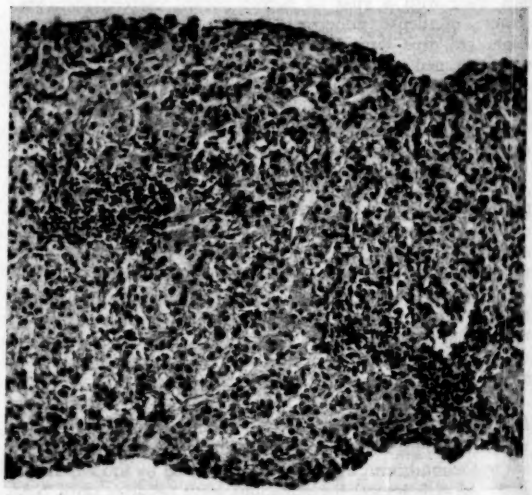

Fig. 2—Portion of liver obtained with needle. (× 115.)

serious: it was often fatal. Terry (1952) related the incidence of hæmorrhage directly to the increased bore of the needle. The risks of liver biopsy have now been minimised by the reduced size of this needle and by the simplicity and speed of the technique employed. Menghini, in a series of 500 biopsies with this needle, encountered no complications.

In our experience so far, results of biopsy by this needle have been satisfactory. There were no complications except for shoulder-tip pain in 1 case.

Our thanks are due to Dr. G. Menghini, Institute of Clinical Medicine, University of Perugia, for demonstrating the technique and for providing us with the needles.

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Preliminary Communication

SKIN TRANSPLANTATION IMMUNITY IN RELATION TO HYPERSENSITIVITY

ALTHOUGH the distinction may eventually prove to be superficial, it is at present useful to divide immunological reactions into two classes—those mediated through orthodox humoral antibodies, and those which seem to depend upon the intercession of activated blood-borne cells. To the former class belong all states of immunity that can be transferred from one animal to another by serum; to the latter—a class which includes the drug allergies and bacterial allergies—belong the states of sensitivity that can be transferred only by lymphoid cells. There is strong evidence that the reaction provoked by homografts of skin (and perhaps by all other "solid" homografts that make direct vascular and lymphatic connections with their hosts) is put into effect by a cellular rather than a humoral mechanism.[1–7]

It is characteristic of the "cellular" immunities that they manifest themselves in the guineapig and in man as dermal hypersensitivities of the delayed type. Our purpose here is to show that the reaction against skin homografts in the guineapig can likewise be made to express itself as a dermal hypersensitivity, and that the state of hypersensitivity can be transferred by activated lymphoid cells but not by serum.

A typical experiment made use of two guineapigs from outbred stocks—a donor (D) and a recipient (R). Four skin homografts from D, with a total area of about 6 sq. cm., were transplanted to one side of the chest of R, a position in which the regional lymph-vessels drain into the axillary nodes. The pairs chosen for ordinary experimental purposes were those in which the homografts broke down in less than 12 days. Two reactions could thereupon be demonstrated: (*a*) the *direct reaction*, in which antigenic matter extracted from the tissues of D was injected intradermally into R; or (*b*) the *transfer reaction*, in which cells expressed from the regional lymph-nodes of R were injected intradermally into D. Both reactions were marked by the development of a tuberculin-like inflammatory response with a latent period of 5–8 hours and a maximum at 24–48 hours.

MATERIALS AND METHODS

The guineapigs were either outbred albinos (usually so chosen that animals D and R came from different breeders) or members of an inbred strain—the Heston strain—which has been proved by skin-grafting tests to be for all practical purposes homogeneous. The technique of skin grafting has been described by Billingham and Medawar,[8] and the behaviour of skin homografts in guineapigs has been the subject of a general study by Sparrow.[9,10] Guineapig R can be sensitised with tissues other than skin, but the use of skin homografts is desirable (*a*) because their donor can be kept alive, and (*b*) because they provide an outwardly visible record of the degree of immunity of the recipient, so that it is possible to eliminate or make special use of the "weak reactors" in which homografts survive for upwards of 15 days.

Cell-free antigenic matter was extracted from the spleen or lymphnodes of guineapig D by the method described by Billingham, Brent, and Medawar.[11]

In bare outline, cells expressed from the lymphoid tissue of the donor were washed successively in 0·15*M* NaCl, 0·05*M* NaCl, and water, and then rendered into a solution in water by exposure to ultrasonic irradiation. The concentration of NaCl was restored to 0·15*M* and the precipitate of desoxyribonucleoprotein, together with miscellaneous cellular debris, removed by centrifugation for 10 min. at about 2000 g. The solution, now wholly free from cells or large particles, was then spun at 25,000 g for 60 min.; the supernatant fluid, containing the soluble protein of the cell and other solutes, was discarded, and the sediment resuspended in Ringer-phosphate at such a concentration that the matter extracted from 1·0 g. wet weight of splenic tissue was contained within 2·0 ml. of the final suspension. (1·0 g. wet weight of splenic tissue yields about 10 mg. dry weight of final sediment.) The suspension is strongly opalescent and, when made from splenic tissue, has a brown or beige tinge that is a minor nuisance when interpreting weakly positive results.

Antigenic substances so prepared are "complete" antigens in the sense that experiments on mice have proved them capable of giving rise to a state of sensitivity indistinguishable from that produced by an equivalent dosage of living cells administered by the intraperitoneal route.

Antigenic matter was injected intradermally, in volumes of 0·1 ml., into the outer aspect of the thigh of R. The quantity injected represented the matter extracted from 50 to 5 mg. initial wet weight of lymphoid tissue (i.e., about 0·5 mg. to 0·05 mg. final dry weight).

Cellular suspensions from the "immune" regional nodes used in the transfer reaction were prepared by teasing out the nodes under about 0·5 ml. Ringer-phosphate and adjusting the concentration of cells to about 100 million per ml. The cells were injected in fluid volumes of 0·05 ml. and in numbers ranging from 4–6 million downwards.

The results of both the direct and the transfer reactions were scored against an arbitrary scale (+ to +++++) which took account of the area of inflammation and of its intensity in terms of reddening, hardness, and swelling.

RESULTS: THE DIRECT REACTION

The "direct reaction" was described above as the reaction that is produced by the intradermal injection into a sensitised recipient (R) of antigenic matter extracted from the tissues of the homograft donor (D).

Thirty independent trials of the direct reaction gave positive results of variable intensity; three others were negative or marginally positive, but the recipients proved

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11. Billingham, R. E., Brent, L., Medawar, P. B. *Transplantation Bull.* (in the press).

to be pregnant and must therefore be discounted.* Animals which gave a +++++ response after injection of the antigen extracted from 50 mg. initial wet weight of D splenic tissue still gave perceptibly positive responses (+ or ++) to the injection of one-tenth of this quantity. The weakest positive response elicited by a high dose of antigen was ++: evidently there were wide variations in the degree of sensitivity of the recipients, though all had rejected their skin homografts within 12 days of transplantation. Experience with mice, however, has shown that even over a wide range of antigenic dissimilarities between donor and recipient the survival-times of homografts may still fall within the range 9–12 days.[14]

The histological appearance of a 24-hour reaction site—kindly interpreted for us by Dr. P. G. H. Gell—was essentially similar to that of a tuberculin reaction.

Living donor cells—preferably lymphoid cells—may be used instead of cell-free extracts to elicit the direct reaction. The reactions were more intensely red and compact than those elicited by cell-free extracts, but table I, based upon three

TABLE I—VARIATIONS BETWEEN THE RESULTS OF THREE TRIALS OF THE DIRECT REACTION (SEE TEXT) USING LIVING D CELLS AS SOURCE OF ANTIGEN. CELL DOSAGES EXPRESSED IN MILLIONS.

Experiment	Cell dose	Score	Experiment	Cell dose	Score	Experiment	Cell dose	Score
55	15	++++	57	30	+++	58	12	+++++
	5	+++		7·5	++		6	+++++
	1·6	++		3·8	±		3	+++
	0·5	+		1·9	±		2	++
	0·16	+						

independent trials, shows that their variability from one animal to another was just as great. The intradermal injection of donor serum into sensitised recipients was ineffective.

The dermal hypersensitivity of four R guineapigs which had each been immunised by four D skin homografts was not strengthened by repeated weekly injections of 2·5 ml. of D blood; in one animal certainly, and possibly in two, the intensity of the reaction declined. This result has raised in our minds the possibility of a "desensitisation" brought about by the action of humoral antibodies. Variations from one pair of guineapigs to another are to be expected, just as the ease of producing "enhancement" varies from one pair of mouse strains to another in accordance with their genetical constitution at the H-2 locus.[15]

It has not been possible to demonstrate the direct reaction in the general body skin or foot pads of mice belonging to several different strains; the results with rabbits have been variable and inconclusive.

As controls for the specificity of the direct reaction, high doses of cell-free antigen were injected intradermally into thirteen non-immune guineapigs, and up to 6 million normal (non-sensitised) lymphoid cells were injected into thirty-seven others. Most of the injections elicited no reaction; a small minority secured a maximal score of +. These are not precise controls, for the inflammatory response provoked by the intradermal injection of antigen might be a non-specific consequence of the state of sensitivity as such. Two exact controls took the form of sensitising an inbred (Heston) guineapig with skin homografts from a non-inbred donor. Although in a sensitive state, the inbred recipient failed to respond to an intradermal injection of antigen extracted from the spleen of a Heston donor; that the antigen itself was active was proved by its power to elicit a strong reaction after injection into a non-inbred guineapig which had been sensitised by skin grafts from a Heston donor. Hence the direct reaction does not merely depend upon the existence of a state of sensitivity: it depends upon the existence of a state of sensitivity directed against the antigens used in the skin test.

* Pregnancy is known to prolong the survival of homografts in rabbits [13] and to subdue the inflammatory processes that accompany the breakdown of homografts in mice.[13] Its effect upon transplantation immunity in guineapigs is not yet known.

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TABLE II—RANGE AND DISTRIBUTION OF SCORES OBTAINED IN THIRTEEN INDEPENDENT TRIALS OF THE TRANSFER REACTION: REGIONAL *v.* CONTRALATERAL NODES. THE NUMBERS ARE THOSE OF THE EXPERIMENTAL ANIMALS

Score	Source of cells	
	Regional nodes	Contralateral nodes
5 or >5	10, 17, 23, 29, 31, 35, 59, 65, 66	10, 65, 66
4	..	..
3	32A, 32B	..
2	19	35
1	..	..
± or 0	21	..

RESULTS: THE TRANSFER REACTION

The "transfer reaction" was described above as the reaction that is produced by the intradermal injection into a homograft donor (D) of cells expressed from the regional lymph-nodes of a sensitised recipient (R).

The transfer reaction produced by the injection of 4–6 million sensitised lymphoid cells is stronger than the direct reaction produced by the injection of concentrated antigenic extracts: it tends to reach its maximum a little later (48 hours as opposed to 36) and to last longer, to be more compact and to give rise to redder, harder, and more prominent swellings. In its extreme form (scored higher than +++++) the reaction may proceed to limited central necrosis.

The scores of thirteen independent trials of the transfer reaction are summarised in table II. We are unable to account for the one animal from which no response of any kind was secured. The evidence of Mitchison [2] and of Billingham, Brent, and Medawar [3] had led us to expect that the reactions elicited by cells taken from the *contra*lateral lymph-nodes would be very feeble. In three of four trials, however (table II), they were just as strong as the reactions elicited by cells from the homolateral (regional) nodes.

Among pairs of guineapigs (D and R) chosen at random it sometimes happens that homografts transplanted from D to R live longer than the usual 9 or 10 days: these are the "weak reactors" referred to in the section on Methods, and they have made it possible for us to show

TABLE III—TRANSFER REACTION. SCORES OBTAINED IN THE DONORS OF "WEAKLY REACTING" PAIRS (SEE TEXT)

Experiment	Homograft survival-time, D→R	Day of transfer of cells, R→D	Maximum score
24	17	17	++
53	20–25	30	±
54	20–25	30	+
33	40–42	17	±
39	>>30	18	0

that the ability of lymph-node cells to elicit the transfer reaction does indeed depend upon the state of sensitivity of the animal from which they were taken.

The tests summarised in table III were carried out either before or immediately after these unusually long-lived homografts had broken down: the transfer reactions were feeble or absent.

The transfer reaction in rabbits (unlike the direct reaction) is particularly violent and long-lasting. All experiments with mice have given negative results, regardless of whether the skin at the time of injection was quiescent or in the midst of a cycle of hair growth.

It is a matter of great theoretical importance to determine whether or not the transfer reaction can be provoked by *serum* taken from sensitised recipients.

Fifteen independent tests were made, including four in which the recipients had been sensitised not only by skin grafts but also by repeated weekly injections of donor blood. Half produced no visible reaction, and none of the remainder secured a response greater than +. The reactions produced by serum were probably non-specific, for they occurred equally often in the thirty-four trials in which normal guineapig serum was injected intradermally into normal recipients. They differed in timing from even the weakest reactions brought about by the transfer of low doses of sensitised cells: a feeble and diffuse inflammation was usually perceptible within 2–3 hours of injection and had faded by the 24th hour.

The transfer of immune lymphoid cells which had been heated to 48·5° for 20 min. produced no reaction greater than +.

In three experiments the procedures of the direct and transfer reactions were combined: 5–7·5 million sensitised regional lymph-node cells from a Heston inbred guineapig R were mixed with 8–10 million normal lymph-node cells (representing "antigen") from the corresponding donor D, and the mixture was at once injected into a third guineapig belonging to the same inbred strain as R. The reaction elicited by the mixture was +++ in all three cases; D cells alone produced a reaction of +, and the sensitised R cells alone produced no reaction whatsoever. Although the reactions produced by the mixture were unexpectedly weak, they were strong enough to justify the obvious supposition that the tuberculin-like inflammatory response which we have been studying is due to some local interaction between antigen and sensitised lymphoid cells.

Controls for the specificity of the transfer reaction require special consideration. In the preceding section it was said that only in a small minority of thirty-seven independent trials did the intradermal injection of normal lymphoid cells into normal animals produce a reaction as great as +. To these may be added the five animals registered in table III, in which lymphoid cells were taken from animals which, though carrying homografts, were not yet sensitive, or only feebly sensitive, when the transfer tests were carried out. These controls do not eliminate the possibility that the transfer reaction might represent some non-specific consequence of the state of sensitivity as such. Six experiments were therefore done in which highly sensitised cells from inbred (Heston) recipients were injected either into the recipient itself or into some other member of the Heston inbred strain. The reactions were negative throughout. In four of the six experiments the sensitised Heston cells were injected intradermally into the homologous donor, to assure ourselves of their ability to provoke a strong reaction.

It should be added that "controls" in which sensitised cells are injected into a third guineapig related neither to D nor R are fundamentally unsatisfactory in design. The third guineapig must often possess antigens in common with D, and should therefore react with a violence proportional to the degree of antigenic overlap between them.

DISCUSSION

At present we have no reason to question the obvious assumption that the "transfer reaction" does indeed represent a passive cellular transference of the state of sensitivity that is disclosed by the "direct reaction". In the direct reaction, an animal in a generalised state of sensitivity is confronted locally with antigenic matter, and in the transfer reaction an animal in which "antigen" is distributed throughout the body is confronted locally with sensitised lymphoid cells. The difference between the two reactions is probably one of tactics and not of principle; both appear to depend upon a local interaction between antigens and sensitised lymphoid cells.

The fact that the homograft reaction in guineapigs can be made to express itself as a dermal hypersensitivity of the tuberculin type, transferable by activated lymphoid cells but not by serum, adds strength to the analogy that has so often been drawn between the two. The homograft reaction, in the form in which we have considered it, evidently belongs to the same general class of immunological reactions as the drug and bacterial allergies, the sensitivities produced by the injection of small quantities of antigen-antibody complex,[16] and that component of autoimmune reactions which is responsible for the lymphocytic infiltration and partial or complete destruction of the tissue against which the immunity is directed.[17–18] All these reactions can be made to manifest themselves as dermal hypersensitivities of the delayed type, and in all of them—including the homograft reaction [2 3 19]—the "antibodies" behave as if they were attached to cells.

The "second set" reaction that is so familiar to students of tissue transplantation—the accelerated athreptic breakdown of a second homograft on an animal which has already rejected a first—is probably a general manifestation of the phenomenon which in guineapigs and man takes the peculiar form of a dermal hypersensitivity. The second-set reaction is analogous to a skin reaction in the sense that it shows up a pre-existing state of sensitivity; it can hardly depend upon a "secondary response" as the immunologist understands that term.

Two other phenomena are almost certainly cognate with the direct form of the hypersensitivity reaction as we have described it in the text. The first is the "recall flare" of Rapaport and Converse,[20] in which the otherwise quiet site of a rejected human homograft becomes swollen and red over the period during which a living homograft subsequently transplanted from the same donor is being rejected. The existence of this recall flare suggests that "homograft antigen" or some component of it still lingers in or around the site of a rejected homograft; and this in turn might account for the extraordinarily long persistence of the state of sensitivity produced by skin homografts and other solid homografts, when compared with the evanescent sensitivity produced by the intraperitoneal injection of dissociated cells (Billingham, Brent, Brown, and Medawar, unpublished work).

The second is the phenomenon first described by F. K. Sanders and since studied in detail by Darcy.[21] Homografts killed by repeated freezing and thawing provoke no reaction on their own account, but become the seat of a brisk infiltration by round cells when they are implanted into rabbits which have been sensitised beforehand by living homografts from the same donor. The dead homografts presumably contain some component of the sensitising antigens present in living homografts. The antigen which we have used in analysing the direct reaction is, however, a "complete" antigen, in the sense that it has the power not merely to reveal a pre-existing state of sensitivity, but also to provoke it in the first place. It has not yet been proved that this complete antigen is necessary to evoke the direct reaction: some fraction of it may suffice.

Our inability to secure the transfer reaction with "immune" serum tells against the view that the inflammatory changes which we have described are due to a reactivity of the Arthus type. The peculiar violence of the transfer reaction in rabbits is nevertheless suspicious, and it is by no means impossible that, with hyperimmunised animals especially, some Arthus-like component should be present.

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SUMMARY

The reaction against skin homografts in guineapigs can be made to express itself as a hypersensitivity reaction of the delayed type.

Two reactions are described: (*a*) a "direct reaction", in which antigenic matter extracted from the tissues of a homograft donor is injected intradermally into a sensitised recipient; and (*b*) a "transfer reaction", in which cells taken from the regional lymph nodes of a sensitised recipient are injected intradermally into the homograft donor.

The transfer reaction is thought to represent a passive cellular transference of the state of sensitivity revealed by the direct reaction. The transfer reaction was not elicited by "immune" serum or by heat-killed lymphoid cells.

The occurrence of these reactions strengthens the analogy between skin transplantation immunity and other immunological reactions that are thought to be mediated through cells.

This work has been helped by grants from the Nuffield Foundation and the British Empire Cancer Campaign. One of us (J. B. B.) is a research scholar of the Medical Research Council.

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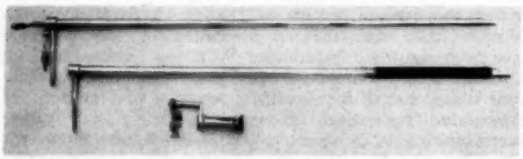
New Inventions

FLEXIBLE ŒSOPHAGOSCOPE

A FEW years ago the Genito-Urinary Manufacturing Company Ltd. made up for me a flexible œsophagoscope which consisted of an outer tube, the distal part being flexible, and an inner tube carrying the light and lens system, which was also flexible in its distal part.

Experience has shown that this complicated and expensive flexible inner tube is not essential, and the œsophagoscope has



been modified using a straight inner tube carrying the light and built-in suction and with a telescope attachment.

To pass the instrument, an œsophageal tube no. 30 FG (18EG 60NE) is threaded through the outer tube projecting about 8 in. from the end, and this enables the œsophagoscope to be passed very easily into the œsophagus of a conscious patient who has had premedication and a local anæsthetic applied to the throat. The œsophageal tube is then withdrawn and the rigid tube is inserted. The telescope attachment is joined and enables an excellent view to be obtained. A biopsy specimen can easily be taken using 60 cm. œsophageal biopsy forceps.

The apparatus is supplied by the Genito-Urinary Manufacturing Company, Ltd., of 28A, Devonshire Street, London, W.1.

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F. AVERY JONES
M.D. Lond., F.R.C.P.

Reviews of Books

Orthopædic Disorders

ERNEST AEGERTER, M.D., professor of pathology and director of the department of pathology, Temple University Medical Centre and School of Medicine, professor of orthopædic pathology, Philadelphia General Hospital; J. A. KIRKPATRICK, JR., M.D., radiologist, St. Christopher's Hospital for Children and Children's Heart Hospital, assistant professor of radiology, Temple University Medical Centre. Philadelphia and London: W. B. Saunders. 1958. Pp. 602. 87*s*. 6*d*.

THIS is one of the most original and praiseworthy orthopædic textbooks that has appeared in recent years. It has been written, not by a surgeon, but jointly by a pathologist and a radiologist. Together they have reviewed all the common (and many of the rare) diseases of the skeleton. In the case of each they have tried to show just how the pathological changes produce the typical clinical features, and how they give rise to radiographic signs.

The main body of the book is prefaced by half a dozen brief chapters on the normal histogenesis of bone and connective tissue. For the sections that follow, the literature has obviously been painstakingly surveyed and abstracted. In consequence even a very experienced surgeon, looking up a condition with which he is familiar, is likely to discover facts previously unknown to him. Yet this is not a "heavy" volume, abounding in paragraphs of small print and lengthy footnotes. What distinguishes this work is that, though its scope is wider than the modest title suggests, it is written throughout in a lucid, consistent, and elegant style.

The Interference Microscope in Biological Research

A. J. HALE, M.B., CH.B., PH.D., lecturer in physiology, University of Glasgow. Edinburgh: E. & S. Livingstone. 1958. Pp. 114. 20*s*.

THE phase-contrast microscope is now widely used for studying transparent specimens such as living cells. The interference microscope is newer and less familiar. The images it produces are free from certain defects inherent in phase contrast, but its most important advantage is that it can be used to make quantitative measurements of optical-path difference. This quantity can be related to the dry mass per unit area of a cell, so that it is now possible to "weigh" parts of cells. In this book the more important instruments and the basic theory underlying their use are described. It should prove useful to biological and medical workers, but its value to the uninitiated might have been increased if more indication of the types of problem which can be investigated had been given.

Collected Papers

Through Pædiatrics to Psychoanalysis. D. W. WINNICOTT, F.R.C.P. London: Tavistock Publications. 1958. Pp. 350. 35*s*.

IN accordance with the established practice of psychoanalysts, Dr. Winnicott has assembled under one cover the articles he has written in various journals. They extend over a period of twenty-one years and are preceded by two chapters, on anxiety and fidgetiness, from an earlier book of his on disorders of childhood. Dr. Winnicott's entry into the field of pædiatrics and the beginning of his personal psychoanalysis occurred in the same year, three years after he qualified. Since then he has become more and more occupied with the psychoanalytical aspects of children's illnesses, and has shown himself to have a strong sense of mission. This is well illustrated in the last contribution in the book—an address to the Eighth International Congress of Pædiatrics—in which he urges that all pædiatricians who wish to treat the psychological troubles of children must take a psychoanalytical training. Dr. Winnicott is one of the leading British psychoanalysts; his innovations in theory have attracted much attention and he has developed a notable skill in conveying his views to large sections of the public. It is therefore to be regretted that, as the bibliography of this book shows, he has disregarded almost entirely the invaluable contributions to child psychology and psychiatry made by non-psychoanalysts. This concentration of interest, however, enables him to present effectively his experience and views.

THE LANCET
LONDON 13 SEPTEMBER 1958

The Report on Prisons

THE latest report on prisons [1] is disquieting yet in some ways encouraging. It is disquieting mainly in its revelation of still more overcrowding: the increase in prison population seems likely to engulf the institutions now in preparation and preclude the improvement expected from them. Between 1952 and 1956 the average number in prisons and borstals dropped from 22,558 to 19,776; but in the early months of this year it was, at 24,700, the highest yet recorded.

One of the notable facts given in the report is that last year the prisons received no fewer than 39,000 men who had not been sentenced. The practice of remanding in custody sometimes seems haphazard, and this high figure strengthens the suspicion that it is often unnecessary. When specialist reports on a prisoner are needed they can often be obtained as easily while he is on bail. Some magistrates seem to remand a man in prison whom they have no intention of sentencing, "to give him a taste of it"; indeed the report mentions that 38–40% of the men imprisoned before trial are not imprisoned after it. This policy may appeal to some, but it must also tend to bring justice into disrepute. Of the men actually under sentence the majority (68%) were in prison for six months or less, while for women the figure was 85%. Perhaps this short-term population could be reduced by wider use of probation (though that excellent service must already be stretched to very near its limit); or by the introduction of the suspended sentence, of which Dr. SCHMIDEBERG recently spoke so enthusiastically from American experience [2]; or, indeed, by increasing the use of our own conditional discharges. For the people sent to prison for a long time, parole gives an excellent incentive and could be used much more widely, as the "Bristol experiment" (placement of prisoners in hostels) has shown.

Among the reasons for imprisonment we note 5539 receptions for non-payment of fine: in 49% of cases the prisoner had *not* (report's italics) been allowed time to pay. Though the use of statistics in penology is full of hazards [3] it is at least worth mentioning that the increase in crimes of violence against the person, which has been greeted with such clamour, is in fact proportionate to the total increase (about a ninth since 1954), except in the 15–21 age-group. Sexual offences, however, show a larger increase in these imprisonment figures (of about a third); larceny remained static and fraud actually decreased. The rise in crime has hit the borstals particularly hard, and the report says that boys have waited for up to six weeks in local prisons for a place in a reception centre. But these are not the only young people in prisons: we read with some horror that 370 boys and girls between 14 and 17 were remanded there; and 1 boy aged 15, and 8 aged 16, were actually sentenced to terms of imprisonment—under the Criminal Justice Act of 1948, section 17(1).

Looking to the report for encouragement, we read of a modest increase in psychiatric services and of successes in a group-psychotherapy unit. Of great interest, too, is the related success of the "Norwich experiment", which comprises the regular evening "association" of large numbers of men with very few officers present. A group atmosphere seems to have been created, and, to quote a governor's report, "the few anti-social and intractable types were contained by this atmosphere, confirming the impression that so far as possible each group must learn to live with and tolerate all types". This remarkable governor also writes of the "identification of officers with individual inmates" which results, and of the value of such personal relationships. This is but one of a series of extracts from the annual reports of senior staff which, in appendix 1, make perhaps the most interesting reading. A new wind really does seem to be blowing through our ancient gaols, and even experienced prisoners are known to admit that things have changed for the better over the last couple of years. Recruitment of the right type of prison officer is extremely important, and the report says little about this, although it is perhaps reassuring to read that, of men approaching the authorities, only 1 in 35 is appointed; of women inquirers, 1 in 63 is chosen.

The commissioners cannot be expected, perhaps, to suggest reforms in such a volume as this; but in our view the essence of progress must be to transform the prison into a truly "therapeutic community". This endeavour will have much in common with what many mental hospitals are trying to do, and the two spheres should become more aware of each other. Such projects would draw much from the wider aspects of Dr. MAXWELL JONES' very interesting work at Belmont, and from Dr. CEDRIC SIMPSON's unit at Wormwood Scrubs. Though the running of a whole prison on something approaching these lines is still a long way off, some enlightened administrations are finding their way there gradually, and they must be watched and encouraged. It really is time that the commissioners and the trade-unions came to some better understanding about contract work in prisons. Too little is done towards rehabilitation, and too many men moulder away doing nothing useful or constructive. The day is long past when we should be content to regard such misery and waste as a proper part of punishment: if the inmates of a Russian prison [4] can earn reasonable wages, which are paid to dependants, why should not ours have an equal chance of regaining usefulness and self-respect? The Russian attitude towards non-political crime is liberal, and in their prisons the internal discipline is said to be handled by a panel of prisoners who sit in judgment on their fellows. This form of group technique has not been tried here yet, though the commissioners report a "working party" of prisoners and very

1. Report of the Commissioners of Prisons for 1957. Cmd. 496. 1958. Pp. 187. 9s. 6d.
2. See *Lancet*, Aug. 2, 1958, p. 249.
3. *ibid.* July 12, 1958, p. 79.
4. *Illustrated*, March 1, 1958, p. 24.

senior officers which discussed round a table problems of prison administration—an event said to be without precedent.

The fact that deficiencies in the prison service are as bad as they are, that research is so scanty, and that progress is so slow does not necessarily put the commissioners under a cloud. They are but doing the best with what they have; and if they have little it is we, the public, that are to blame. This branch of therapeutics, though very important to our society, is given low priority.

Sphincter and Hiatus

UNTIL quite recently our great protector that lies between the stomach and the gullet might well have been called the Sphinx—even the Sphinx of Sphinxes—because its behaviour seemed so enigmatic. The name is more apt than it may seem; for the Sphinx of Thebes was not only a riddler but also a *sphincter* or strangler (of those who could not solve her riddles). Today the riddles of the cardiac or œsophageal sphinx are happily being solved. Apart from the personal experience of each one of us that, as a rule, there is some effective check to the reflux of stomach contents into the œsophagus, we now feel more sure, from the work of FYKE et al.,[1] ATKINSON et al.,[2] and CREAMER and PIERCE,[3] among others, that there really is a sphincter around the lower end of the gullet, even though it has not yet been displayed by dissection. There seems to be a band of higher muscular tension around the lower 2–3 cm. of the œsophagus which resists the pressure gradient between abdomen and thorax. It relaxes as the cup is raised to the lips in drinking, and so allows fast-moving liquid to pass through before the peristaltic wave arrives at the cardia and peters out there. It also relaxes at an early stage in the simpler act of swallowing. These physiological features are thought by CREAMER and PIERCE [3] to explain why certain careful investigators in the past have failed to identify the sphincter.

Normally this zone of higher muscular tension lies partly in the abdomen, below the diaphragmatic hiatus. (As a recording tube is withdrawn from the stomach, the position of the hiatus is indicated by a fall in pressure and by a simultaneous inversion of the respiratory waves in the tracing.) Being thus in contact with the abdominal pressure, the sphincter responds when this increases. As in a bucket of fluid, pressure in the abdomen is greatest at the lowest point (CANNON,[4] FYKE et al.[1]), and even tilting of the body by 15° will raise the pressure around the intra-abdominal portion of the cardiac sphincter, perhaps also evoking protective contraction. In people with hiatus hernia the abdominal pressures are carried into the intrathoracic part of the stomach: above this, in a proportion of cases, one can detect a sphincteric zone in which pressure is increased, and above this again there is the sudden drop and inversion signifying a thoracic pattern. Sometimes the sphincteric zone shows little or no increase in tension, and in these cases acid reflux readily occurs. ATKINSON et al.[2] have found good correlation between the clinical evidence of reflux and the graphic evidence that the sphincter is poorly developed. If this finding is fully substantiated by further experience, it will explain why hiatus hernia presents in so many different ways—particularly as regards the presence or absence of acid reflux—and why patients may have reflux though they have no hernia at all. The evidence of pressure tracings is the more valuable because in some cases the presence of a hiatus hernia is not revealed by radiography. Moreover, pressure tracings and cinefluoroscopy in patients with hiatus hernia have also shown (CROSS et al.[5]) abnormal muscular behaviour in other parts of the gullet, particularly muscular overaction in the lower part, together with underaction in the upper part. Correlation of these with dysphagia will sometimes provide a satisfactory explanation for this symptom, in cases of œsophagitis, ulcer, or stricture. In the same way, OLSEN and CREAMER [6] have elucidated the distinction between achalasia and diffuse spasm.

Despite the doubts raised so cogently by Dr. HOUGHTON in his letter last week,[7] we shall be surprised if the pressure tracing does not turn out to be an important means of investigating patients with hiatus hernia and other disorders of the gullet. Even with a large hernia, a good sphincter (if such exists) should prevent reflux and so render surgical repair unnecessary, provided other symptoms such as pain and eructation are not serious. Where there is reflux and the sphincter is poor or absent, it may at first sight seem useless to repair the hernia, for the sphincter will still be weak. But if the sphincter is moved to below the diaphragm, it may be reinforced by the abdominal pressure—which explains why some cases of reflux are cured by simple surgical repair. (BOTHA'S [8] conception of the rosette of mucosal folds rendered active or erect by the muscularis, as check against reflux, is complementary, not alternative to nor exclusive of the idea of the sphincter.) Mere tightening of the hiatus, even with creation of an acute angle between the lower end of the gullet and the fundus of the stomach, is of more doubtful value against reflux. Again, in patients whose symptoms—particularly acid reflux—recur after surgical repair, the pressure tracing may prove to be of great value. If, in a patient with troublesome reflux, the repair is found to be intact but the sphincter poor or absent, a difficult situation will be evident. Perhaps some drastic measure to diminish gastric acidity will be required; perhaps a surgical attempt should be made to fashion a check against reflux, which will nevertheless allow vomiting when necessary; or perhaps the jejunal segment of MERENDINO and DILLARD, [9] interposed to act as a physiological sphincter, may be the answer.

Obviously the subject is very far from being exhausted. Apart from the necessity for substantial

1. Fyke, F. E., Jr., Cody, C. F., Schlegel, J. F. *Gastroenterologia*, 1956, **86**, 135.
2. Atkinson, M., Edwards, D. A. W., Honour, A., Rowlands, E. N. *Lancet*, 1957, ii, 1138.
3. Creamer, B., Pierce, J. W. *ibid.* p. 1309.
4. Cannon, W. B. Mechanical Functions of Digestion; p. 227. New York, 1911.
5. Cross, F. S., Kay, E. B., Johnson, G. F. *J. thorac. Surg.* 1957, **34**, 736.
6. Olsen, A. M., Creamer, B. *Thorax*, 1957, **12**, 279.
7. *Lancet*, Sept. 6, 1958, p. 525.
8. Botha, G. S. M. *Brit. J. Surg.* 1958, **45**, 569.
9. Merendino, K. A., Dillard, D. H. *Ann. Surg.* 1955, **142**, 486.

verification of the above findings, many questions may be asked. For example, why should some patients, whether they have a hiatus hernia or not, have a competent intrinsic sphincter, and others none? May there be some drug which could restore tone to a lost sphincter, or in reverse could relax the action of one that is too energetic? All in all, it seems that the riddling function of this sphinx remains, particularly when her strangling powers have been lost.

Excision or Resection for Rectal Cancer?

DOES preservation of anal function sometimes jeopardise cure after operation for rectal carcinoma? MAYO et al.[1] have compared survivals after anterior resection and abdominoperineal excision, and have found, surprisingly, that 60% of 476 patients traced after anterior resection had survived for five years, compared with 52% of 580 traced after excision. It might be suspected that there was bias against excision by the inclusion in the second group of many late cases; but almost exactly half the resection group had metastases (231 cases with, 245 without) compared with rather less than half in the excision group (273 with, 307 without); so the bias, if any, lay against "conservative" resection. What then of level?—for surely excision must be a more effective means of cancer clearance when the growth and its metastases lie below the peritoneal reflection? Again surprisingly, the five-year-survival statistics favour resection, not only in the absence but also in the presence of lymph-node involvement, when the lesion was situated in the zone 6-14 cm. from the dentate line: 2 inches is the agreed minimal length distal to the growth for adequate mural clearance, and conservative resection cannot be performed for growths lower than this. It is only fair to observe that the resection group consisted of patients who had been operated on with the hope of cure, and did not include patients who had been operated on with the aim of palliation; whereas there is no evidence that there was such a distinction in the abdominoperineal group.

GOLIGHER,[2] though in favour of anterior resection for growths at the rectosigmoid or intraperitoneal part of the rectum, will not countenance its routine use, with the aim of cure, for tumours at a lower level. This, in fact, represents the current British view. MORGAN [3] has observed that the crude survival-rate of 66% after 110 radical anterior resections for lesions of the intraperitoneal rectum and rectosigmoid, when corrected (81%), is little different from the corrected survival-rate for a comparable group submitted to combined excision (78%). With so little difference as regards survival it is proper to select the operation which is less disabling; and it must be borne in mind that a colostomy is not the only disadvantage of excision—impotence is a sequel in a quarter of the men.[4] The experience of BUTLER [5] and of MUIR [6] is similar. All agree that resection is the operation of choice for lesions in the upper third. That the operation is valuable at lower levels (6-14 cm. from the dentate line) for palliative purposes when hepatic metastases are present is not denied; and a case can be made out for its use at this lower level for the aged in all circumstances,[7] since colostomy management is fraught with difficulty in the elderly, who so often live in lonely squalor: many rectal growths are slow to develop, and even imperfect eradication may serve the allotted span of an old patient; and the operative risk of resection is lower than that of excision in the elderly. Otherwise there are no British advocates of resection as an elective curative procedure at this lower level.

Yet the Mayo Clinic is not alone in its reports of favourable results of resection for lesions below the peritoneal cul-de-sac: BEST and RASMUSSEN [8] regard it as appropriate for three-quarters of patients with lesions 5–12 cm. from the anal margin, and find that survival is comparable to that after excision. Furthermore they observe that, whereas excision in their hands is followed by impotence in 75% of cases, after resection the figure is only 25%. Nevertheless it is difficult to understand why resection should be as effective as a wider excision in an area where lymphatic spread is known to occur laterally as well as proximally, unless perhaps our conception of the pathological progression is wrong. HERMON TAYLOR [9] takes the view that blood-stream spread is the most important factor in prognosis, and that when it occurs it has usually done so before the institution of treatment—thus rendering extensive lymphatic dissection useless. This may be so; but it has yet to be demonstrated, though venous invasion has been shown in as many as 50% of specimens.[10] As a result of the controversy which has continued throughout the post-war decade, resection is now established as the operation of choice for lesions of the upper third of the rectum. In the next decade controversy is likely to centre on the surgical treatment of lesions of the middle third.

Contraceptives

THE doctor seeking reliable information on contraceptives has no official source to turn to: on this subject the *British Pharmacopœia* is silent. Yet the need for informed guidance is great; for some manufacturers may be tempted to make excessive claims, and these are not readily disproved. Accordingly the Family Planning Association does a notable public service by publishing its *Approved List of Contraceptives*. The contraceptive substances listed must comply with the Association's requirements about quality, efficiency, and harmlessness, and standard of presentation. The list, besides being an indispensable source of information for doctors, pharmacists, and nurses, acts as a stimulus to manufacturers to develop effective contraceptives and to present them soberly. The latest edition [11] includes an explanation of the purpose of the list and the criteria for approval.

1. Mayo, C. W., Laberge, M. Y., Hardy, W. M. *Surg. Gynec. Obstet.* 1958, **106**, 695.
2. Goligher, J. C. *Ann. R. Coll. Surg. Engl.* 1958, **22**, 311.
3. Morgan, C. N. *Proc. R. Soc. Med.* 1957, **50**, 1050.
4. Goligher, J. C. *ibid.* 1951, **44**, 819.
5. Butler, E. C. B. See *Brit. med. J.* July 26, 1958, p. 226.
6. Muir, E. G. *Aust. N.Z. J. Surg.* 1958, **27**, 174.
7. Brooke, B. N. See *Brit. med. J.* July 26, 1958, p. 226.
8. Best, R. R., Rasmussen, J. A. *J. Amer. med. Ass.* 1957, **164**, 731.
9. Taylor, H. See *Brit. med. J.* July 26, 1958, p. 226.
10. Barringer, P. L., Dockerty, M. B., Waugh, J. M., Bargen, J. A. *Surg. Gynec. Obstet.* 1954, **98**, 62. Madison, M. S., Dockerty, M. B., Waugh, J. M. *ibid.* 1954, **99**, 170.
11. Approved List of Contraceptives. Published by the Family Planning Association, 64, Sloane Street, London, S.W.1. 1*s.* 6*d.*

Annotations

JOURNEY INTO SPACE

PROGRESS in the exploration of space is rapid. This year we have seen the establishment of satellites in orbital flight around the Earth, and the safe return of two dogs from a height of 279 miles. It seems likely that a multi-stage rocket may soon make the 250,000-mile journey to the Moon.

To place an object in orbit around the Earth, velocities of 18,000 m.p.h. are needed, and to carry an object out of the Earth's gravitational field the velocity of escape must be about 25,000 m.p.h. Rockets, powered conventionally, can attain such speeds only by using large amounts of fuel. The American Vanguard, for instance, needs 1000 lb. of rocket and fuel for every 1 lb. of payload. This expensive ratio of propellant-weight to vehicle-weight is at present the most serious impediment to manned space flights. Development of new rocket fuels, possibly nuclear, would render much more feasible a vehicle heavy enough to contain a man with his necessary equipment and yet with power to bring him safely back. At the present rate of progress such a vehicle may be designed within the next few years.

It is reasonable to suppose that man's first journeys into space will be in an Earth satellite, and this will long precede any attempt at inter-planetary travel. Whether man can in fact orbit around the Earth is the first problem which " space medicine " seeks to answer. Space medicine is the youngest of the medical sciences. Fathered by physiology and nurtured by aviation medicine, it has now freed itself of the taint of miscegenation with science fiction. Some aspects of its scope are dealt with in a symposium published in the July issue of the *Journal of Aviation Medicine*.

Conventional powered flight has taken man well above the respirable portion of the Earth's atmosphere, which extends a mere 5 miles. Survival in the tenuous air of the outer atmosphere depends on pressurisation and the maintenance of a high concentration of oxygen. Brief sorties beyond the atmosphere involve no new respiratory problems, except the provision of safety measures if pressurisation should fail or emergency " bail-out " prove necessary. The atmosphere, however, has functions other than the provision of oxygen under pressure. The relatively constant temperature of the Earth depends on its atmospheric shell; the atmosphere also acts as a shield against cosmic and auroral radiation and the assaults of meteors. Man, beyond the atmosphere, will be exposed to extremes of temperature, a yet unknown amount of radiation, and the possibility of collision with meteoric bodies. The intensity and penetrance of the radiations will be of crucial importance in determining the possible duration of exposure of man to these fields.[1] The equipment necessary for protection, for the provision of oxygen, and for pressurisation will impose a weight penalty intolerable with present methods of propulsion.

If space travel is to become a reality, thought must be given to the provision of food and water within acceptable weight limits. On Earth there is a natural cycle for the conservation and re-utilisation of the materials necessary for life. This cycle, involving the passage of individual elements through animals, plants, and bacteria, takes a long time but is complete and self-perpetuating. To economise in weight, some form of closed ecological system for the re-utilisation of all the body wastes must be developed. Clark [2] says: " this task of developing an adequate closed food cycle is the most difficult and, hence, the most significant task that must be completed before man can begin extended space voyages ". The value of such research is not restricted to space travel. In many circumstances on the Earth and oceans the chances of survival could be increased by artificial systems for recycling human wastes.

The fundamental work on these problems can be undertaken in the laboratory, but the problems associated with increased and decreased gravity are less amenable to a ground experimental approach. During the high-speed take-offs necessary to reach orbiting and free heights, the acceleration forces will impose on the space traveller weights 4–8 times that of gravity. These stresses can be readily simulated on the ground by the human centrifuge; and there is little doubt that, exerted for short periods, they are tolerable: much depends on the position of the person and the clothing worn. On the other hand, the lack of gravity or " weightlessness " which will develop when the space craft becomes a celestial body floating freely in the Earth's gravitational field is far less easily investigated. Gerathewohl and Stallings [3] have succeeded in producing " weightlessness " or zero gravity for short periods by flying an aircraft in parabolic arcs at altitudes of 17,000–25,000 feet. They found that, as predicted, there were disturbances in the otolith organs, which were manifested by ocular illusion. With further investigation it may be found that the psychological and physiological effects of " weightlessness " are intolerable. If this is so it may be possible to provide the space vehicle with some artificial device for producing the sensation of gravity.

HYDATID DISEASE

THE dog is the optimum definitive host of the tapeworm *Echinococcus granulosus*, while the domestic and wild ruminants, and ungulates such as the ox, pig, deer, and particularly the sheep, are intermediate hosts for the larval stage or hydatid, which develops in the lungs or liver after the ingestion of ova from an echinococcus-infested carnivore. Man may also ingest the ova, and human hydatidosis has been heavily endemic in certain areas of the world, such as Iceland, New Zealand, Southern Australia, and parts of South America, where an intimate sheep-dog-man relationship prevails. It is not without reason that human hydatidosis has been termed *la maladie des mains sales*.

A long-recognised public-health measure to avert human hydatid disease is to prevent dogs being infected with the tapeworm, and this involves ensuring that the infected viscera of slaughtered animals are destroyed. Dramatic results have been achieved in Iceland and Australia by vigorous promulgation of this policy. Another measure—the regular administration of anthelminthic drugs to every dog—has helped to diminish the regional canine reservoirs of echinococcus.

In Britain hydatidosis in man and domestic animals is relatively rare; the incidence in sheep and in man is highest in South Wales. It is important that this relative freedom from hydatidosis be preserved, and we are therefore disturbed to learn that New Zealand ox livers containing hydatid cysts have been imported into this country, presumably for pharmaceutical purposes or animal feeding; as many as 3000 bags of livers have been imported in one week, and apparently up to 20% have

1. Schaefer, H. J. *J. Aviation Med.* 1958, **29**, 492.
2. Clark, C. C. *ibid.* p. 535.
3. Gerathewohl, S. J., Stallings, H. D. *ibid.* p. 504.

been infected. Even more disturbing is the report [1] that many livers were being disposed of to retail butchers without mention of their diseased condition; it is obvious that small cysts embedded within the liver substance would not readily be detected.

There seems to be no statutory bar to the importation or sale of these infected livers, provided they are not intended for human consumption; but the Ministry of Health, if satisfied that there is an urgent need in this country for pharmaceutical products manufactured from animal livers, might consider whether it would not be best to insist that the livers be processed in their country of origin. An even more serious gap in public-health law is that there is nothing to prevent a retail butcher exhibiting for sale as pet food meat scraps and organs unfit for human consumption, on the same stall as normal sound meat. This undesirable practice seems to be growing, and there is urgent need for legislation to make it an offence.

ABNORMAL BETA-GLOBULINS

DEVELOPMENTS in the research on abnormal human hæmoglobins in man have been followed by the demonstration of similar polymorphism for other proteins. It was known that cow's milk contained two β-lactoglobulins, but this observation had usually been made on pooled milk. When samples from individual animals were examined it was found that the two lactoglobulins were distributed as polymorphic characters, some cows producing only one of the two globulins and others both—representing homozygous and heterozygous phenotypes.[2 3] In the plasma of man there are two haptoglobins [4]—α_2-globulins capable of binding free hæmoglobin [5]—which also are distributed as if they are determined by allelic genes. Smithies [6 7] also found in human plasma three different β-globulins which he called β-B, β-C, and β-D. There is evidence that the formation of these three β-globulins is genetically controlled, and Smithies suggests that each may be determined by one of three allelic genes. He observed the patterns C, BC, and CD. C was most commonly found in the Canadians he investigated, but C plus B occurred in 1% of Canadians and C plus D in about 4% of American Negroes. The phenotype CD was even commoner in Australian aboriginals, in whom one example of a fourth phenotype (D) was discovered.[8] The phenotypes B and BD, which are also possible, have so far not been described.

Harris et al.[9] working in Britain, have studied the β-globulins of man by means of the discontinuous buffer system of Poulik.[10] In a series of 153 Africans from the Gambia they found four examples of CD. Two types of D β-globulin were identified which differed slightly but distinctly from one another in their electrophoretic behaviour; these have been named D_1 and D_2. In 139 English people no examples of the CD_1 or the CD_2 phenotype were found; but the combination B plus C was found in two people. The two B β-globulins were not identical, so there seem to exist a B_1 and a B_2. The family of the person with the B_1C phenotype was further investigated, and a pedigree was constructed which showed that the β-globulin B_1 is genetically determined, and that the members of the family with the B_1C phenotype are heterozygous for the appropriate gene.

Obviously the human serum β-globulins deserve to be studied with the close attention that has been given to the hæmoglobins; they are likely to be of equal interest to the biochemist, the geneticist, and the anthropologist. Polymorphism is the outcome of the selective advantages and disadvantages in a particular environment of inherited characters which are determined by allelic genes and which are neither dominant nor recessive in the phenotype. In the case of the hæmoglobins much interest has been taken in the resistance of carriers of the trait for sickle-cell hæmoglobin against the lethal effect of malignant malaria. It will be of special interest to see which selective advantages the various β-globulins confer against diseases due to infection, climatic influences, and malnutrition. A polymorphism for serum-β-globulins has also been demonstrated in cattle,[11 12] in which there are three different proteins determined by a three allele system resulting in six phenotypes. In cattle the geographical distribution of one of the β-globulins suggests that it is associated with tolerance of the more severe northern climates.

THE "MEDICAL OFFICER"

As an independent journal "for medical men and women in the Government and municipal services"—a group which, though influential, is not large—the *Medical Officer* has attained its golden jubilee [13] only because it has always been so well worth reading. The difficulties of producing a weekly journal for a small group are very real, and this is the only public-health weekly in the world; but the benefit to readers is real too, for a periodical which comes out once a week can "combine some of the liveliness and topicality of a newspaper with the more sober and lasting qualities of a scientific journal." The particular attractiveness and value of the *Medical Officer* derives largely from the Elliston family, its hereditary editors. George Elliston, son of a physician in Ipswich and nephew of the first M.O.H. for that town, was on the staff of Sir Joseph Causton & Sons, the printers, when he founded the journal in 1908; and later, as secretary of the Society of Medical Officers of Health, member of Parliament, chairman of the health committee of the City of London, chairman of the board of management of the London School of Hygiene, and in many other ways a power in public health, he was a remarkably well-informed as well as a naturally able editor—with what his old friend Sir Allen Daley describes as "the journalistic 'nose' for finding out any unusual development and the barrister's flair for pungent exposition." Since Sir George Elliston's death in 1954, his eldest son, Mr. Lewis Elliston, who had long been working with him, has carried on the journal with the same mixture of perception, friendliness, and zest. We wish it many more years of its valuable service to medicine.

Prof. R. H. S. THOMPSON, Prof. E. J. WAYNE, and Prof. B. W. WINDEYER have been appointed members of the Medical Research Council.

Lieut.-General Sir BENNETT HANCE, medical adviser to the Commonwealth Relations Office and a former director-general of the Indian Medical Service, died on Sept. 5 at the age of 71.

Prof. W. M. FRAZER, medical officer of health for Liverpool from 1931 to 1953, died on Sept. 8 at the age of 70.

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1. *Times*, July 5, 1958.
2. Aschaffenburg, R., Drewry, J. *Nature, Lond.* 1955, **176**, 218.
3. Aschaffenburg, R., Drewry, J. *ibid.* 1957, **180**, 376.
4. Smithies, O., Walker, N. F. *ibid.* 1955, **178**, 1265.
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7. Smithies, O. *ibid.* 1958, **181**, 1204.
8. Horsfall, W. R., Smithies, O. *Science*, 1958, **128**, 35.
9. Harris, H., Robson, E. B., Siniscalo, M. *Nature, Lond.* 1958, **182**, 542.
10. Poulik, M. *ibid.* 1957, **180**, 1477.
11. Ashton, G. C. *ibid.* p. 917.
12. Ashton, G. C. *ibid.* 1958, **182**, 370.
13. *The Medical Officer*, 72, Fleet Street, London, E.C.4. Golden jubilee number, Sept. 5, 1958.

Special Articles

THE COST OF ORAL IRON PREPARATIONS IN FAMILY AND IN HOSPITAL PRACTICE

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TWENTY years ago Davidson and Fullerton (1938) clearly established that, for correcting iron-deficiency anæmia, ferrous sulphate was as effective as any of the iron preparations then available (ferrous carbonate, ferrous chloride, colloidal iron, iron and ammonium citrate) and had a considerable advantage in cost. During the past ten years a number of organic preparations of iron have appeared on the market and gained wide popularity. Further studies have therefore been undertaken to ascertain which oral preparation is the most suitable in regard to therapeutic efficiency, incidence of toxic effects, and cost.

A therapeutic trial by O'Sullivan, Higgins, and Wilkinson (1955) showed that when ferrous sulphate, ferrous gluconate, or ferrous succinate was given in doses containing equivalent amounts of elemental iron (210 mg. daily), each caused a similar rise in the hæmoglobin level.

Kerr and Davidson (1958a and b) have recently reported the results of two controlled investigations. In the first, ferrous sulphate, ferrous gluconate, ferrous gluconate plus vitamin C, and control tablets containing lactose were administered to groups of women in the last trimester of pregnancy. The amount of elemental iron given daily in each preparation was 105 mg. The mean rise in the hæmoglobin level in the three groups receiving the iron-containing tablets was approximately similar, and there was no difference in the incidence of gastro-intestinal "side-effects" between these three groups or between the treatment groups and the control group. In a second trial ferrous sulphate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and control tablets containing lactose were administered in turn to groups of nurses. With the dosage of iron given, none of the iron-containing preparations caused more side-effects than the control tablets. By using known and unknown control tablets it was established that the symptoms complained of by the nurses were mainly psychological in origin.

Both in family and in hospital practice, iron-deficiency anæmia is one of the diseases most commonly encountered, and very large amounts of iron are prescribed annually for its treatment. The choice of oral iron preparation is determined partly by the doctor's own clinical experience and partly by the pressure of advertising. Since ferrous sulphate, ferrous gluconate, and ferrous succinate, when given in tablets containing equivalent amounts of elemental iron, have similar therapeutic efficiency and similar toxicity, the problem of their relative cost assumes great importance. This is particularly the case today when there is an urgent need for economy in the National Health Service.

Accordingly, we have inquired into the comparative costs of the widely used non-proprietary and proprietary iron tablets, and the frequency with which they are prescribed.

Comparative Cost of Various Iron Tablets

Information about the cost of the more popular iron tablets in present use in family practice is summarised in table I. The four proprietary preparations are designated "proprietary 1, 2, 3, and 4".

Column A shows the basic price of 100 tablets. Because of the system of costing, the allowance which the chemist receives from the Government for the purchase price of a drug used in dispensing N.H.S. prescriptions is not always the same as the net cost. Hence the former figure has been given. The prices of non-proprietary preparations have been obtained from the National Health Service, Scotland, Drug Tariff (January, 1958) and Amendments (to April, 1958), and those of proprietary preparations from The Retail Chemist Trade Price List of Proprietary Articles (1957) and Supplements (to March, 1958), the latter prices being adjusted to accord with the Drug Tariff system of payment.

Most iron preparations are cheaper to the chemist if purchased in bulk. For proprietary preparations deduction is made if the chemist endorses the prescription to the effect that he has dispensed the 100 tablets from a larger pack. Throughout the table, therefore, the reduced cost of 100 tablets of the proprietary preparations if dispensed from a 1000 pack is shown in parentheses. For non-proprietary preparations, however, the figure shown in column A is always paid, regardless of the size of pack. In some circumstances the proprietary preparations are subject to 30% purchase-tax. Purchase-tax has not been included in the prices given in column A, but where applicable has been listed separately in column B.

Column C gives the total amounts which the chemist receives for dispensing 100 tablets on an N.H.S. (Scotland) prescription. These figures (to the nearest halfpenny) have been derived as follows:

Net cost of 100 tablets (column A) plus oncost allowance (25% of net cost), plus 1*s.* 7*d.* dispensing fee, plus $1\frac{9}{10}$*d.* container allowance, plus refund of purchase-tax if applicable.

The cost to the N.H.S. in Scotland of a prescription for 100 tablets of each of the iron preparations is shown in column D. This amount is the figure given in column C minus 1*s.* (the prescription charge paid directly to the chemist by the patient).

The prices to patients of 100 iron tablets if purchased at a chemist's shop without a prescription are listed in column E.

TABLE I—COMPARATIVE COST OF 100 TABLETS OF DIFFERENT ORAL IRON PREPARATIONS

Oral iron preparation	A Basic price of 100 tablets of different oral iron preparations	B Purchase-tax on 100 tablets	C Allowance to Chemist for dispensing 100 tablets on N.H.S. prescription	D Cost to N.H.S. of prescription for 100 tablets (column C minus 1*s.*)	E Cost to patient of 100 tablets if purchased at chemist's shop without a prescription
Ferrous sulphate:					
Ferrous-sulphate tablets *B.P.*	1*s.* 3½*d.*	..	3*s.* 4½*d.*	2*s.* 4½*d.*	2*s.* to 3*s.*
Ferrous-sulphate compound tablets *B.P.C.*	5*d.*	..	2*s.* 3*d.*	1*s.* 3*d.*	1*s.* 3*d.* to 2*s.*
Proprietary 1	1*s.* 0½*d.* (4*d.*)	3½*d.* (—)	3*s.* 4½*d.* (2*s.* 2*d.*)	2*s.* 4½*d.* (1*s.* 2*d.*)	1*s.* 10*d.*
Ferrous gluconate:					
Ferrous-gluconate tablets *B.P.C.*	2*s.* 5*d.*	..	4*s.* 9*d.*	3*s.* 9*d.*	4*s.* to 5*s.*
Proprietary 2	3*s.* 10*d.* (2*s.* 9½*d.*)	.. (—)	6*s.* 6½*d.* (5*s.* 3*d.*)	5*s.* 6½*d.* (4*s.* 3*d.*)	7*s.* 4*d.*
Proprietary 3	3*s.* 1½*d.* (3*s.* 1½*d.*)	11½*d.* (—)	6*s.* 7*d.* (5*s.* 8*d.*)	5*s.* 7*d.* (4*s.* 8*d.*)	5*s.* 9*d.*
Ferrous succinate:					
Proprietary 4	3*s.* 1½*d.* (2*s.* 5*d.*)	11½*d.* ($8\frac{7}{10}$*d.*)	6*s.* 7*d.* (5*s.* 6*d.*)	5*s.* 7*d.* (4*s.* 6*d.*)	5*s.* 5*d.*

Figures in parentheses denote reduced cost of 100 tablets if dispensed from a 1000-tablet pack.

TABLE II—SURVEY OF NATIONAL HEALTH SERVICE PRESCRIPTIONS DISPENSED IN SCOTLAND DURING MAY, 1957

Total number of N.H.S. prescriptions dispensed = 1,689,505.
Number of prescriptions in sample studied = 10,495 (0·6% of total).
Number of prescriptions for oral iron preparations in sample = 230 (2·19% of sample).

Number of prescriptions for different oral iron preparations and number of tablets prescribed

Oral iron preparation	No. of prescriptions	Total no. of tablets prescribed	Average no. of tablets per prescription
Ferrous sulphate:			
Ferrous-sulphate tablets *B.P.*	23 (*10%*)	2268	98·6
Ferrous-sulphate compound tablets *B.P.C.*	14 (*6%*)	1466	104·7
Proprietary 1	17 (*7%*)	1550	91·2
Total	54 (*23%*)	5284	..
Ferrous gluconate:			
Ferrous-gluconate tablets *B.P.C.*	39 (*17%*)	3176	81·4
Proprietary 2	61 (*27%*)	5196	85·2
Proprietary 3	14 (*6%*)	1068	76·3
Total	114 (*50%*)	9440	..
Ferrous succinate:			
Proprietary 4	62 (*27%*)	5732	92·5

Total number of iron tablets prescribed in sample = 20,456.
Average number of tablets per prescription in sample = 88·9.
Ratio of prescriptions for ferrous sulphate to prescriptions for ferrous gluconate plus ferrous succinate = 1 (23%): 3 (77%).
Ratio of prescriptions for non-proprietary preparations to prescriptions for proprietary preparations = 1 (33%): 2 (67%).

For proprietary preparations the retail price is fixed by the manufacturers. For non-proprietary preparations the figures given represent the average prices charged by several chemists in Edinburgh at whose shops inquiry was made.

This table shows that the cost to the Government of a prescription for 100 ferrous-sulphate tablets ranges from 1*s.* 2*d.* to 2*s.* 4½*d.* For ferrous gluconate the range is 3*s.* 9*d.* to 5*s.* 7*d.* and for ferrous succinate it is 4*s.* 6*d.* to 5*s.* 7*d.* If a patient purchases 100 iron tablets at a chemist's shop without a prescription the price charged will vary from 1*s.* 3*d.* for "Ferrous sulphate compound tablets *B.P.C.*" to 7*s.* 4*d.* for one of the proprietary preparations of ferrous gluconate. The cost to a patient of 100 iron tablets dispensed on a "private" prescription varies from chemist to chemist, but is usually more than the cost of the same preparation purchased over the counter or supplied on a N.H.S. prescription.

The difference in cost of oral iron preparations to the hospitals is still more striking. Since most preparations are supplied to hospitals by manufacturers under contracts which are confidential, the full range of prices cannot be quoted. Furthermore, the expenditure on iron tablets may be greatly reduced if very large quantities are purchased. Hence the cost of iron tablets is relatively less in a large hospital which caters particularly for acute medical, surgical, and obstetric cases than in a small hospital which caters for the chronic sick. We are satisfied, however, from information received from hospitals and manufacturers that the price to hospitals of proprietary and non-proprietary preparations of ferrous sulphate is only 3*d.* to 4*d.* per 100 tablets, whereas ferrous gluconate costs at least three to six times as much and ferrous succinate six to ten times as much.

Frequency with which Different Iron Tablets are Prescribed

Family Practice

In a survey undertaken by the Department of Health for Scotland of 10,495 N.H.S. prescriptions dispensed by representative chemists throughout Scotland during the month of May, 1957, it was found that 2·19% (230) of the prescriptions were for iron tablets. This is in agreement with the observation of Dunlop, Inch, and Paul (1953) that about 3% of their large sample of prescriptions dispensed in Scotland during October, 1951, were for iron—a figure which included mixtures and injections as well as tablets. Table II shows the frequency with which different preparations were prescribed and the average number of tablets ordered. The terms "proprietary 1, 2, 3 and 4" refer to the same preparations as in table I.

Only 23% of the prescriptions dispensed in family practice were for ferrous sulphate. The remainder were for ferrous gluconate (50%) and ferrous succinate (27%). Two-thirds of the prescriptions were for proprietary preparations of iron: ferrous sulphate (proprietary 1) 7%, ferrous gluconate (proprietary 2 and 3) 33%, and ferrous succinate (proprietary 4) 27%.

During the month under consideration (May, 1957) 1,689,505 N.H.S. prescriptions were dispensed in Scotland. Although the sample studied represented only 0·6% of these, it probably gives a fair indication of the pattern of prescribing, since the prescriptions were obtained by random sampling. If this is so, the total number of N.H.S. prescriptions for oral iron tablets for family practice in Scotland in a typical month will be about 38,000 $\left(\frac{203 \times 100}{0{\cdot}6}\right)$, and, since the average number of tablets ordered per prescription is about 90, the total number of iron tablets dispensed per month is between 3 and 3½ million.

Hospital Practice

The number of hospital beds in Scotland is 65,802 (May, 1958), of which 22,036 are in mental hospitals. A questionnaire was sent to ten general hospitals in different parts of Scotland, and (because a large proportion of beds are for mental patients whose iron requirement was thought likely to be low) to four large mental hospitals. Information was requested regarding the quantities of ferrous-sulphate, ferrous-gluconate, and ferrous-succinate tablets, both proprietary and non-proprietary, used in a recent twelve-month period. The replies are summarised in table III. There was considerable variation in the prescribing habits in the different hospitals; but, taking them as a whole, ferrous gluconate seems to be used

TABLE III—SURVEY OF THE USE OF IRON TABLETS IN A RECENT 12-MONTH PERIOD IN REPRESENTATIVE HOSPITALS IN SCOTLAND

—	No. of beds in Scotland	No. of beds surveyed	% of total no. of beds	No. of iron tablets used annually			Total
				Ferrous sulphate	Ferrous gluconate	Ferrous succinate	
General hospitals ..	43,766	8,010	18·3	810,000*	815,000	135,000	1,760,000
Mental hospitals ..	22,036	4,063	18·4	44,000	37,000	1000	82,000
Total ..	65,802	12,073	18·3	854,000 (*46%*)	852,000 (*46%*)	136,000 (*8%*)	1,842,000

* The figures for numbers of iron tablets are to the nearest thousand.

almost as often as ferrous sulphate, and, although ferrous succinate has not gained wide popularity, large quantities of it are also being prescribed.

If the hospitals which cooperated in the survey are typical of the remainder, the total number of iron tablets consumed annually by hospital patients in Scotland is likely to be about 10 million, of which 46% are ferrous sulphate, 46% ferrous gluconate, and 8% ferrous succinate.

Summary and Conclusions

Ferrous-sulphate tablets, with or without added trace elements, proprietary or non-proprietary, are the cheapest preparations of iron at present available for oral medication. Since ferrous sulphate raises the hæmoglobin level as effectively as ferrous gluconate and ferrous succinate, and, when given in comparable doses of elemental iron, is no more liable to cause side-effects it is the preparation of first choice for oral iron therapy.

In hospital practice the amount of ferrous sulphate prescribed (46%) is slightly less than the total for the newer organic preparations (54%). The prices of the different tablets vary considerably, depending on the manufacturer and on the quantity purchased; but, using the lowest price for each preparation, the cost of iron tablets to the hospital service in Scotland each year can be calculated to be at least £3000.

In family practice, however, ferrous sulphate is prescribed considerably less frequently (23%) than the more expensive organic preparations of iron (77%). From the data present in this paper the cost of the iron tablets used by the National Health Service in Scotland is calculated to be £6500 per month.

If ferrous sulphate were always prescribed in preference to ferrous gluconate and ferrous succinate the saving to the N.H.S. in Scotland would be, at a conservative estimate, about £1800 in a year for hospital practice and £3250 a month for family practice—a total of almost £40,000 per annum.

If it is accepted that the ferrous compounds mentioned above are similar in therapeutic efficiency provided that the daily intake of iron in each preparation is the same, and if it is agreed that the standard effective dose of ferrous sulphate is one tablet three times daily (180 mg. of elemental iron), then the equivalent dose of ferrous gluconate and ferrous succinate would be five tablets per day (175 mg. of elemental iron). On this basis the use of ferrous sulphate would lead to an even greater saving to the Health Service than the amounts suggested above.

We wish to thank Sir Kenneth Cowan, of the Department of Health for Scotland, for giving us permission to publish the prescription survey and for providing details of the number of hospital beds in Scotland. We are also grateful to those physicians and pharmacists in different parts of Scotland who supplied us with data regarding the iron tablets used in their hospitals.

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CONSULTANTS AND OTHER SPECIALIST STAFF IN HOSPITALS

THE Ministry of Health and Department of Health for Scotland have issued tables that will be of special interest to those intending to train as specialists.

Table I (not reproduced here) shows the age-distribution at June 30, 1956, of consultants and senior hospital medical officers practising in the various specialties. It shows also the numbers of paid sessions undertaken by the consultants and S.H.M.O.s in each specialty for each year of birth.

Table II shows the numbers of consultants in each of the specialties year by year from 1949. The corresponding figures for senior hospital medical officers are not available.

Table III shows the number of senior registrars in each specialty on June 30, 1956, at the various stages of their training. The column headed "Others" includes those holding "transitional" posts.

All the figures relate to England, Wales, and Scotland.

TABLE III—SENIOR REGISTRARS IN GREAT BRITAIN ON JUNE 30, 1956

Specialties	Training plan					Others*	Grand total
	1st year	2nd year	3rd year	4th year	Total		
General medicine	39	40	30	27	136	68	204
Diseases of the chest	12	18	11	8	49	4	53
Mental health	49	32	20	9	110	12	122
Neurology	2	3	2	5	12	2	14
Pædiatrics	4	8	7	5	24	12	36
Radiology	25	15	16	8	64	3	67
Radiotherapy	4	5	4	3	16	..	16
Physical medicine	3	4	2	1	10	..	10
Pathology	16	17	14	16	63	40	103
Infectious diseases	2	1	..	1	4	2	6
Dermatology	2	3	4	7	16	13	29
Venereology	1	1	1	1	4	2	6
Ophthalmology	19	18	12	5	54	11	65
General surgery	47	41	31	26	145	66	211
Anæsthetics	39	19	11	4	73	6	79
Neurosurgery	2	6	2	2	12	3	15
Plastic surgery	1	4	2	2	9	8	17
Thoracic surgery	5	5	6	3	19	10	29
Orthopædic surgery	22	18	8	6	54	11	65
Ear, nose, and throat surgery	17	9	9	5	40	7	47
Obstetrics and gynæcology	17	24	17	9	67	34	101
Totals	328	291	209	153	981	314	1295

* Includes 93 honorary and 26 part-time senior registrars.

TABLE II—NUMBER OF CONSULTANTS IN EACH SPECIALTY AT VARIOUS DATES SINCE DEC. 31, 1949 (GREAT BRITAIN)

Date	General medicine	Diseases of the chest	Mental health	Neurology	Pædiatrics	Radiology	Radiotherapy	Physical medicine	Pathology	Infectious diseases	Dermatology	Venereology	Ophthalmology	General surgery	Anæsthetics	Neurosurgery	Plastic surgery	Thoracic surgery	Orthopædic surgery	Ear, nose, and throat surgery	Obstetrics and gynæcology	Totals
Dec. 31, 1949	755	216	449	53	166	327	85	49	495	50	127	89	331	927	496	37	30	49	252	312	424	5719
Dec. 31, 1950	831	250	504	53	202	378	93	57	526	52	136	101	341	943	602	39	32	57	269	328	439	6233
Dec. 31, 1951	857	266	532	59	208	400	101	61	541	48	135	99	342	948	655	42	33	66	293	341	449	6476
Dec. 31, 1952	904	310	566	61	214	414	108	70	581	51	142	97	351	986	714	44	36	81	320	339	473	6862
Dec. 31, 1953	905	340	595	67	222	436	112	75	631	60	145	94	342	982	748	46	43	89	328	346	473	7079
Dec. 31, 1954	924	344	616	68	226	447	116	74	646	59	146	93	340	987	782	48	48	91	335	350	485	7225
June 30, 1955	932	346	633	69	228	455	120	73	659	58	146	93	341	988	797	49	50	93	339	353	493	7315
June 30, 1956	946	347	640	70	229	468	127	77	689	56	150	92	339	988	815	52	50	97	353	347	495	7427

Consultants practising in more than one specialty have been included under each. Table includes honorary consultants.

HOSPITAL COSTS

IN England and Wales the cost of our hospitals has grown from £219 million in 1949–50 to an estimated £421 million in the present financial year. This is a colossal sum, but the gross national product—the most straightforward measure of the country's total resources—has risen even more rapidly, as was clearly shown by Abel-Smith and Titmuss.[1] Part of the increased cost merely reflects the falling value of the pound. But other factors are at play. First, the population of England and Wales has increased in the past ten years. Secondly, there are more elderly people in the country, and their demands on hospital services are greater than those of the general population. Thirdly, the hospital service has been slightly expanded, and it is dealing with many more patients. Staffed beds have increased in the decade from 448,057 to 476,870; and admissions have increased from 2,937,000 in 1949 to 3,794,000 in 1957. Fourthly, the length of stay, especially in maternity and mental cases, has been curtailed; people are getting well faster, and it is usually the early days of hospital care, when so much diagnostic work has to be done, that cost the most. Finally, modern hospital techniques are more expensive than those of former years.

NEW YORK

So much for the local scene; but England and Wales are not the only countries with problems of cost. In the New York area the seventy-four voluntary hospitals and convalescent homes report an operating loss of $23,500,000 for 1957—an increase of $3,550,000 over the 1956 figure.[2] This deficit takes no account of, on the one hand, receipts from philanthropic sources and income from investment and, on the other, hospital depreciation, interest on debts, and money spent on research and medical education. It was estimated that the hospitals' net loss, including all income, was in the region of $6 million; this estimate includes an allowance of 5% for plant depreciation. Meanwhile the operating income, including revenue from patients and from auxiliary activities which produce income, went up 6·8% to $176,000,000; and the operating costs rose 8% to almost $200 million.

In the New York area hospital admissions have increased by 41% since 1946. In the production of motor-cars, the greater the number that run along the production line, the lower the cost of each; but in hospital service the reverse holds good: speed and skill add to the expense. Obviously no-one would want to change this beneficent advance, and, as one administrator said, "the deficit is a badge of honour". But hospital care, like pleasure, has to be paid for some time or another. Many administrators in the New York hospitals and elsewhere feel that, if only the potential patients could be taught to appreciate the benefits of scientific care in reducing the period of illness, as well as cutting down suffering and anxiety, they would be ready to pay the enhanced price. Dr. Martin Steinberg, the executive director of Mount Sinai Hospital, says this [2]:

"One cannot define hospital service in terms of so many dollars a day or in terms of a specific quantity. When the patient purchases hospital services, the quantity and its cost are determined only by the requirements of his illness and the capacity of the hospital to fulfil them."

But this partly begs the question. Admittedly some patients would be able, and even more would be willing if they were able, to pay enhanced costs; but what about the many for whom the hospital bill spells ruin, or at least a crippling reduction of income, perhaps at the very time when extra benefits of food and fresh air are most desirable?

CANADA

The problem of hospital costs has been faced realistically in several of the Provinces of Canada. The *Journal of the Canadian Medical Association* has issued the report of an interesting and instructive symposium which deals with various approaches.[3]

Alberta

In Alberta [4] the first step towards hospital insurance was to establish a free public-ward service for all maternity cases. This was heartily approved by the public, because the overwhelming majority of the women have their babies in hospital. The profession also gave considerable support to the plan. The next stage was to introduce what became known as the "dollar-a-day" plan, through which each patient pays that amount for a public-ward bed, the remainder of the cost being met by the municipality with help from the provincial Government. The people strongly supported the scheme, but there was some resistance from the municipalities on the ground that the provincial contribution was not enough. Nevertheless the entire province was covered within two years.

This advance into the realm of public medical care was in time felt to be insufficient. Many patients still had a heavy hospital bill to discharge on account of the cost of medicines, operating-room charges, and diagnostic services. By 1945 these extras were absorbed by an additional flat-rate charge of a dollar a day, and this extension in its turn proved highly popular. The waiting-lists became longer—in relation to short-term investigation up to as much as 22%.

Saskatchewan

In Saskatchewan [5] the Hospital Services Plan has been in operation since 1947. The scheme was designed to remove the financial deterrent to hospital care and also to ensure that the hospitals received enough funds to provide an adequate service. Most persons who have lived in the province for six months are required to join the scheme, unless they already qualify for complete hospital care through other approved plans. Those taking part represent more than 92% of the population. The one test is the need for hospital care, and the Plan pays for public-ward accommodation and all incidental costs such as X-ray, anæsthetics, and physiotherapy. At the beginning of 1957 the limit was raised to $10 per day. In the same year the hospital tax was fixed at $20 for self-supporting persons, with $5 for dependent children. The maximum tax payable per family was increased to $45.

On the whole the Plan has worked very well although it contributes little towards the capital costs of construction or extension, beyond the federal grants of $2000 per active bed and $1500 for each convalescent bed. These grants have been matched by the provincial Government. The Plan is administered by the Department of Public Health and by staff employed by the Government. The Hospital Association and the medical profession are purely advisory.

In 1956 the average number of days in hospital for all patients was 10·4. Patients remaining in hospital for over thirty days represented 5% of all cases, and yet accounted for more than 31% of the patient-days. This emphasises

1. Abel-Smith, B., Titmuss, R. M. The Cost of the National Health Service in England and Wales. London, 1956.
2. *N.Y. Times*, June 2, 1958.
3. *Canad. med. Ass. J.* 1958, **78**, 747–773.
4. Morgan, H. V. *ibid.* p. 747.
5. Brown, J. L. *ibid.* p. 749.

the need for more studies on the treatment of long-term illness, and especially on the care of these patients, wherever possible, outside the " acute " wards of the general hospital.

In 1947 the total expenditure on the Plan was about $7·5 million. By 1956 the figure had risen to over $22 million, and the average cost per case (excluding the newborn) rose in these ten years from $46·61 to $124·46.

British Columbia

The main features of the arrangements in British Columbia are as follows [6]:

1. All persons, after a year's residence, are entitled to hospital benefits.
2. Payments cover the acute phases of hospital care but not chronic illness.
3. Standard ward care which is covered includes the use of the operating-room and nearly all drugs and services except anæsthetics.
4. For outpatient services required within twenty-four hours after an accident a charge of $2 is made.
5. Inpatients (except welfare cases) are charged a coinsurance-rate of $1 per day.
6. There are limited insurance benefits for residents of British Columbia who have to enter hospitals outside the province.

In the early days of the scheme attempts were made to levy individual premiums and, later, to make payroll deductions, but in 1954 these were replaced by payments from general taxation by means of raising the social-service tax from 3% to 5%.

In summing up the effects of Government-financed hospital insurance in British Columbia Watson [6] makes the following points in relation to hospital costs:

A look at the " business " growth of the insurance scheme shows an expanding picture. Since 1948 hospital beds have increased by 37%, patient-days by 50%, and staff by 80%. During the same period expenditure on hospital insurance has risen well over 100%. On the other hand, salaries and wages have gone up 225%. " The doctor, thinking of medical services and not of the big business statistics, sees a lop-sided progress. The hospitals have been helped out of debt. Their staff has increased. The hospital worker has had his standard of living increased remarkably. Ironically, however, the beds available, the patients treated and the diagnostic and therapeutic advances have accounted for the smallest percentage of the increase."

Federal Legislation

The position in Canada is likely to change as a result of the Hospital Insurance and Diagnostic Services Act of 1957.[7]

This enabling measure provides for a contribution by the Federal Government of 50% of the cost, more or less, to any province which agrees to make insured hospital services available, on uniform terms and conditions, to all residents of the province so entitled under provincial law, and without charge to the residents except a general charge by way of premium, or other amount unrelated to a specific service, and except authorised charges. The Act does not cover hospitals for the tuberculous or the mentally ill. Capital expenditure and debts are also excluded. Each province will decide how it will raise its share of the costs—whether by premium or taxation.

One effect is likely to be an increased demand for hospital care—up to a " plateau " estimated at about 7–8 beds per 1000 population.

WIDER LESSONS

These findings direct attention to matters requiring further consideration in Britain and other countries. First, we must be ready to examine hospital costs on a basis which offers real opportunities for comparison between one country and another. Secondly, the rise in costs should be carefully related to other features in the national economy, including the general increase in prices, the growth of population and the demand for institutional services, and, not least, the urge towards higher standards of living. It is by no means easy to devise criteria of cost which will satisfy the demand for accurate comparison between one country and another; but the idea is worth far more than a passing glance.

Such a study should help us to detect economies that might be made without loss of efficiency, and particularly the point at which hospital care could well be exchanged for home care. We might then be better able to decide what types of patient could be transferred, on good medical grounds, from the highly specialised attentions of the " acute " ward to simpler and perhaps more appropriate accommodation.

6. Watson, H. N. *ibid.* p. 751.
7. See Turner, J. G. *ibid.* p. 768.

The Wider World

MEDICINE IN THE NEW INDIA

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FOR two years, from early 1956 until early 1958, I was in India, having been invited there under the Colombo Plan. Working entirely among Indians, with Indians and for Indians, and counting as a class I officer of the Government of India, I obtained an insight into medicine in the country such as is not possible for anyone paying a brief visit.

Western medicine on the British model has been established in India for a long time: for example, the Government General Hospital in Madras claims to have been founded in 1677, and much of the present building was designed by Florence Nightingale. British methods of teaching predominate, British textbooks are used, and English is still the medium of instruction. The present generation of educated people think and talk in English, and this language is unlikely to be replaced by Hindi for a long time, especially in South India where Hindi is regarded as the more foreign.

Indeed British methods persist in every activity, especially in government and administration and perhaps it is the persistence of this edifice that has prevented the country from sinking into chaos. Unfortunately, however, the system was not designed to give freedom at the periphery; and the vested interests of people who have been in it for a long time have increased its rigidity. Europeans long in the country told me how little was the difference to them when the few British at the top were replaced by Indians; and indeed there were few to replace. 77% of foreign investment in India is British, and the number of British technicians and business administrators in the country is greater than ever. Indians regard the British domination as one episode in their country's long history—inevitable in the circumstances and nothing to be ashamed of. Newspapers always refer to their present " independence ", and there is no double talk of " freedom " or " liberation ". Sastri [1] presents the background to this.

1. Sastri, K. A. N. A History of South India. London, 1955.

British policy in medicine has been continued in many ways. Thus one of the recommendations of the committee on the medical services, formed in 1941 with Lieut.-General Sir Bennett Hance as chairman, was that institutes for postgraduate training should be established throughout the country, where there were suitable facilities and teachers, and these are now being set up. The Institute of Obstetrics and Gynæcology is at the Government Hospital for Women and Children in Madras and I was invited there as first professor of pathology. It was intended originally that these institutes should eventually move to Delhi and form part of a central Institute of Medical Sciences; but now a much smaller central institute is starting up, while the peripheral ones are to continue.

Some improvements in the organisation of medicine have been introduced recently by the central Government. Thus the standard of the qualifying examinations has been made uniform at an internationally accepted level. The diplomas of the various States have been abolished, retaining only the M.B. of the universities, and central inspection of the examinations has been undertaken. There is, of course, reciprocity with many Commonwealth countries. A number of new colleges have been opened, new buildings being erected, and senior staff trained specially, many of them abroad. Though unable to visit any of these colleges, I heard much about them from younger colleagues who hoped to transfer to them.

THE DOCTORS

The doctors among whom I was working were a hand-picked bunch, but I found the general standard of medicine higher than I had expected. In his own surroundings the Indian is far more adaptable and resourceful than he often appears in an alien environment, nor is he as self-conscious. After the first shyness had worn off I found postgraduates well informed and energetic in discussion; and, as with us, methods of teaching are far more by informal rounds and discussions than by formal precept and lecture. The Indian doctor works among ignorant and depressed people who regard him as a superior being; patients are too poor to pay much and there is heavy competition from cheap quacks. (These include practitioners of Ayurvedic "medicine", a system based on the old humours [2] but encouraged by the Government.) It is surprising, then, that almost all the doctors remain keen and alert and continue to think of what will be best for the individual patient. They tend to emphasise their membership of the international army of medicine at the expense of local knowledge: thus they will quote British and American statistics when these are not applicable (although often there are no comparable Indian figures). However, they know well enough the circumstances of their own compatriots and I myself found that adaptation of Western knowledge to the social conditions of the patients was not difficult, given a readiness to inquire and to learn. Indians of education are very willing to help in this, and do not object to inquiries made in the proper spirit, even when concerning religion. I heard of an understandable tendency among undergraduates to regard the humble villager as a lower species, but this is evidently soon rectified by the chastening discipline of practice.

I was told that there are about three times as many candidates as places at the medical schools. A fifth are reserved for women and others for members of the "scheduled castes". The curriculum is based firmly on the British model. Some interesting experiments with it are being made at the Christian Medical College at Vellore; but this, like all missionary enterprises now, works under a strong and continuous barrage of criticism and discouragement from the Government. The whole concern is a free gift from private individuals in America, Australia, and Britain, and its senior staff is drawn from those countries, but its achievements are claimed as "Indian" [3].

CONDITIONS OF WORK

Government schemes are by no means all helpful to progress. Not only is the administration rigid but the Oriental genius for red tape and procrastination, especially over finance, has to be experienced to be believed. My own work was much curtailed by this.

Most unfortunately the semi-military control of personnel has been retained, and even senior people are "posted" (with no warning and without being consulted) by the D.M.S. who rules the medical service of each individual State in the Indian Union.

Promotion is entirely by seniority within a specialty; there is virtually no competition for appointments, and in a hospital all authority is in the hands of the senior member of the staff as superintendent. Because people are moved so often, the staff of a hospital becomes quite unstable in its composition. Except for those still belonging to missionaries, all the free hospitals, including the teaching ones, and almost all the research institutes, are run by the State Governments. Even in the non-clinical departments of the medical schools, the appointments are made by the local D.M.S. and accepted by the university. The new postgraduate institutes are attached to universities, and the senior jobs in them rank in the academic hierarchy; but here again almost all appointments are made by the local D.M.S. Wherever they may have graduated, the postgraduate students are admitted to the higher degrees of the local university. We had graduates from as far apart as Cambridge and Calcutta. There is nothing corresponding to the diplomas of our Royal Colleges.

The pay of doctors is extremely low, even by local standards. A specialist in his 30s is unlikely to have more than about £300 a year and can get little extra from part-time private practice. A senior professor may get as much as £900 a year without private practice. The retiring age is still 55. Of course, some senior people make large incomes in private, and many distinguished consultants have no hospital appointment. Nursing-homes and private hospitals of all grades flourish. Many of the younger people resign from the hospital service as soon as they have their higher degrees. The diplomas of our Royal Colleges are still very popular, and I am sure will continue to be so, especially as they are the only alternative to the Government's rigid system.

Pay becomes worse the further one goes from the centres; yet it is at the periphery, among the unchanging villages that cannot afford to support doctors, that they are needed most. One is always reading exhortations from elderly politicians to educated young people to go to work in the villages; but they are expected to go about on foot, live in mud huts, cut themselves off from all hope of refresher courses and of promotion, and be content with a pittance. Such dedicated souls exist in India as in all countries, but naturally there are far too few to do what is essential. In obstetrics the position is very bad because

2. Shastri, M. K. *J. Ind. med. Prof.* 1955, **2**, 616.

3. Witts, L. J. *Lancet* 1957, i, 1343.

far more women than men are being trained. Almost all are married, and, though they are able to go on working, they cannot leave their husbands to go to the villages. India being a democracy, a member of the hospital service is free to resign, and he will certainly do so rather than be posted to a village. He can get better pay abroad, e.g., in the U.K. or Malaya—and so many of the best young people are exported. This applies to other fields besides medicine. I found that gold-field technicians were still being attracted to South Africa (of all places) by the pay.

THE HOSPITAL AND INSTITUTE

We admitted about forty postgraduates each year, nominated by the medical services of the various States of the Indian Union. They had a year's course for a diploma, which almost all obtained, and about half went on for a second year to sit for the Madras M.D., which about five obtained. The average age of students was rather high at first, but is coming down as people who obtain priority by seniority are passed out. As the hospital undertook about 13,000 deliveries and 5000 operations each year, they had plenty of material.

Fortunately money had not been lavished to make a show place for distinguished visitors, and we still had the old open airy wards with wide verandahs. The poor-class Indian does not understand or like a bed, and so is kept in one only as long as the nurses find it more convenient. After this there is a mat on the floor. Many of the patients came from long distances; all were poor and mostly illiterate; few received antenatal or postnatal care; and reattendance and follow-up were virtually impossible with our resources. Anyone needing long-continued treatment had to be kept in for the whole time, and immediate admission from outpatients was essential. Some had been seen by a doctor outside; others had been treated by such people as the local barber's wife, who is the hereditary midwife in an Indian village; while others simply arrived on foot or in a rickshaw and told their tale. The number of patients thus has to be, and can be, expanded considerably as required. A new building to house laboratories, library, &c., is projected, but fortunately is to be in the old simple style.

The average family income of patients was about Rs.40 (£3) per month, and their degree of anæmia and of infestation corresponded. The average age at marriage was just over 14 years and at first delivery just under 20.[4] Prolapse was common and severe and also vesicovaginal fistula. Much stress is laid on "family planning", but many came for sterility too because it carries grave social disabilities.

The patients stood surgery very well despite severe malnutrition and anæmia. After a normal delivery the woman would be sent home in forty-eight hours. Of course, we saw many specifically tropical conditions—filariasis, malaria, amœbic dysentery—but this hardly affected gynæcological treatments, which differed only in small ways from those seen in the West. The medical staff of all grades were most keen and competent. Their practice was based on advanced British and American ideas and they easily adapted their Westernised knowledge to the background of their patients. Most of the seniors had been abroad for work and study, usually to the U.K., U.S.A., Canada, or Sweden.

I found the standard of laboratory medicine good wherever I went in India, but it is confined almost exclusively to academic centres. Buildings and equipment are simple—except in a few very favoured places—but adequate. I felt that on the whole they had spent the small available funds to good advantage and had avoided frills. Biochemistry is largely in the hands of science graduates, but not bacteriology. Blood-transfusion is neglected. The old-established research institutes continue in being and some new ones have started, especially in the all-important subject of nutrition; but there are still too few and they are hampered by the arbitrary selection of staff. Our institute was very research-minded, and the suggested investigations were usually carried out by juniors specially posted by the D.M.S. on request. These young people had a very varied background but seemed to tackle the work well under supervision. The amount of Indian original work which reaches print seems to be very small compared with the effort put into it, but it is hard to see just why this should be so.

The best technicians in our sense of the term are junior science graduates, classified as "assistants". Lower grades are not well trained, and indeed most ancillary staff are of poor quality because deliberate policy keeps the number of jobs high and the pay low. This may still be necessary in India, but the Western visitor becomes irritated by the rows of peons asleep on benches and of clerks who cannot type accurately. Many of the routine chores are done by junior medical staff who stay too short a time at them to become skilled.

Of nursing I was unable to judge; but I understand from visiting experts, and from those who have been under their care, that Indian nurses can be described as moderate. They are kind and attentive, but most are lacking in advanced techniques. Their pay and conditions of service are relatively rather worse than those of doctors. Many more are needed urgently, especially midwives.

The main object of the institute was, of course, teaching; and for this we had adequate facilities, firstly in the flood of material, secondly in the quality of the teachers, and thirdly in the equipment. Much of the teaching was informal, but seminars and lectures were held. We had a cool lecture room, projectors, tape recorders, and good photographic equipment, with a trained "photo-artist" who also assisted students to prepare their "books" of cases—an examination requirement obviously based on that for the M.R.C.O.G. We had a small museum which we recatalogued and enlarged. We took a fair number of the world's journals relevant to the work, but there had not been time to build up a library. We all relied heavily on the library of the British Council, which has a very good and up-to-date medical section, containing many of the summaries of recent work which are so useful to post-graduate students. Indeed the British Council is very active and influential in India.

Unfortunately necropsies were almost impossible to obtain. Junior doctors shrink from asking for them, but the seniors have even attempted to introduce legislation to facilitate them. I had not realised how important they are until I was without them.

GENERAL BACKGROUND

Social

Working with enlightened and friendly colleagues and students, it was often difficult to remember how different was their background from my own; but we must do this if we are to understand their problems and especially if we are to help Indians who come to this country and are uprooted from their own culture.

The ancient organisation of caste and family was described once and for all by Dubois,[5] and the account has been brought

4. Rewell, R. E. *J. Obstet. Gynaec. Brit. Emp.* 1957, **64**, 821.

5. Dubois, J. A. Hindu Manners, Customs and Ceremonies (revised by H. K. Beaumont). London, 1908.

up to date by Thomas.[6] Some recent writers, such as Carstairs,[7] have implied that it is now confined to a small section of the people; but, in South India at any rate, it is still almost universally valid, although in the cities there is little evidence of it to the casual observer. The great majority still live in the old way; all the sons, with their wives and children, remain under their father's roof; the wives do not speak to their husbands in the presence of their mother-in-law, and marriages are arranged by the parents. Unless destined to go to a university, girls in enlightened families are still married off at the minimum legal age of 16, while in poorer and more backward families this minimum is generally disregarded. Like so much recent legislation apparently directed against ancient wrongs, that against child marriages is so worded as to be easily disregarded in practice.[6] Despite forecasts to the contrary (e.g., Wheeler [8]) this way of life has probably become more rigid since independence. The various " communities " do not mix with each other in their own homes, and I am sure that this —not European standoffishness [9]—is why mixing between Indians and Europeans has always been so difficult. Outside their homes, mixing is now general in the cities.

Economic

India is an overcrowded country with an impoverished soil and few industries as yet. The cow is sacred: innumerable semistarved brutes crop all the young vegetation, producing very little milk, and lack of wood leads to their dung being used as fuel instead of as manure. The only animal protein that many people will take is curd made from the milk of cow or buffalo, but its scarcity makes this expensive. Meanwhile the population increases.

India then must industrialise, and faces the now familiar problem of how to do this rapidly without inflation and profound social dislocation. Medicine cannot claim an undue slice of increased productivity; but, without disparaging what has been achieved recently, I am sure that much more could be made of the resources available. The methods of administration are extremely wasteful; and in any case it is an insult to responsible, trained, and honest people to tie them up with red tape as is done. This treatment has to be experienced to be believed. Doctors in hospital must be allowed much more say in non-clinical and administrative matters than at present; they should also have some security of tenure in senior posts, and better methods of promotion must be devised. With the present expectation of life the retiring age should be raised to 60: by preventing waste of skill this would save money. Most important of all, the periphery must be made attractive. It is there that the real work is to be done, and it is there that at present nobody will go if he can possibly avoid it. On the practical side medicine is keeping up well, and fortunately practitioners are striving to maintain a place well in the mid-stream of present-day medical thought. To continue the use of English will certainly help to keep them there. (The only subject in which no regard was paid to accepted opinions appeared to be fæcal hygiene.)

NEED FOR HELP

India remains a poor country and needs help to raise herself. Western experts are welcomed, and every facility was given me by the people with whom I was actually working; the atmosphere was most friendly and I soon felt myself to be one of the team. In spite of the shortage of trained people, there is no room in India now for the European doctor to settle: Indians intend to keep their own jobs for themselves and cannot understand how we in Britain admit people from other Commonwealth countries or European refugees. But organisations like the Colombo Plan allow British doctors to give their help for a time, without personal loss and indeed with gain in many ways.

I am extremely glad that I went to Madras. The officials of the Commonwealth Relations Office, both in the U.K. and in India, were most helpful, and my pay and conditions of service were very good. Pay is very important, because a high standard of living is necessary for us to maintain efficiency in a difficult climate. My conditions certainly were very much better than those of people whom I met working for the World Health Organisation.

6. Thomas, P. Hindu Religion, Manners and Customs. Bombay, 1956.
7. Carstairs, G. M. *Lancet* 1958, i. 1217.
8. Wheeler, M. Still Digging. London, 1955.
9. Toynbee, A. J. A Study of History (abridged by D. C. Somervell); vol. 9. London 1957.

Conferences

WORLD FEDERATION FOR MENTAL HEALTH

THE 11th annual meeting of the Federation, held in Vienna from Aug. 24 to 29, had nearly 500 participants from 34 countries. Its main theme was uprooting and resettlement.

Dr. BROCK CHISHOLM (Canada), the president, in an address called Man's Responsibility in the World, spoke of the continued existing of second, third, and perhaps fifth class citizens, who are deprived of certain rights; and of the ridiculous people who still judge by such signs as colour of skin. There are very few communities without some degree of discrimination. Describing the way in which children are being prejudiced in early life, he recognised five abilities as necessary for the assumption of responsibility in the world today:

1. The ability to face and accept facts and act upon them.
2. The ability freely to change attitudes independently of parents and forbears, and without guilt and anxiety.
3. The ability to live without discrimination and prejudice.
4. The ability to love without discrimination and prejudice.
5. The ability to make discoveries, and to appreciate what is discovered.

He drew attention to the pitifully small proportion of research effort that is devoted to mental health and to human behaviour.

Refugees and Immigrants

Dr. MARIA PFISTER (W.H.O.), discussing Resettlement as a Sociological Problem, pointed out that the more coercive the conditions in which resettlement takes place, the stronger the regression in the behaviour of both parties; and that in periods of crisis this will bring out stress that is only latent at other times. Another very important factor is the degree of uniformity or diversity of the social ideal held by the two parties.

She came to the general conclusion that, whenever possible, there should be a phase of planning and preparation for migration for both parties. In any resettlement there must be a " catalysing " team which is briefed with knowledge of the factors influencing both parties, and it should be constantly asked, " how does one resettle? " Mass action is the arch-enemy of mental health in resettlement. Families must be sent as single units, and there must be no separation of children from parents. In all resettlement processes there is a great need for time, and this is a need which few Europeans know instinctively.

Mr. ELFAN REES (World Council of Churches) gave some impressive facts about the 40 million people driven from their homes since the close of the second world war. They form a third force in society—the proletariat of the dispossessed. He reminded the meeting that, besides a

camp psychosis, there is an out-of-camp psychosis—the attitude of refugees who do not want to leave a camp.

Prof. ERIK H. ERIKSON (U.S.A.) spoke of the normal identity crises—for example, during adolescence or in any major change of status, or during involution. Just as normal people will react differently to these identity crises, so will refugees. There is a positive side to the refugee position, in that a person who has never felt uprooted may never have had a strong positive sense of being at home. If he has never been isolated, he may never have found an identity. To become an alien may for some people be to become mature.

Dr. H. STROTZKA (Austria) outlined the work of the Austrian Society for Mental Hygiene in establishing teams to tackle the mental-health problems of the 183,000 refugees passing through Austria. Counselling services and other medical attention was available in such a way that, though there was much disturbed behaviour, no refugee was sent to a mental hospital. It was seen that such admission would hopelessly compromise the future of the individual refugee. From experience Dr. Strotzka emphasised the terrible effects of lack of information and communication, in spreading mistrust and paranoid attitudes.

Prof. DAN L. ADLER (U.S.A.) described the Psychological Problems of the Voluntary Migrant to Australia.

A study of the response patterns of more than 400 immigrants of various nationalities was made, and compared with over 200 Australian children's responses. This showed how the various patterns of family behaviour, such as the mother's or the father's autonomous behaviour, tended to approximate to the general Australian pattern, from quite diverse original patterns, within about six years. Also, it seems possible to interpret parental dissension as an index of general tension. The main hope of the Australians in respect of the refugees is in the children rather than in the existing families.

Prof. JOHN C. SAWATSKY (Canada) talked about the settlement of 400,000 immigrants in the metropolitan Toronto community, where they now form almost a third of the population. Favourable conditions allow the immigrant families to make a simple transition, but it is for the children to complete this process.

Dr. KENNETH SODDY (scientific director of the Federation) summarised the reports of the 13 discussion groups on various aspects of the refugee situation, the film discussion group, and the special conference of immigration officials which was held alongside the main meeting. This conference was attended by senior health and welfare officials of the main countries with extensive immigration programmes. This informal conference of Governmental representatives made a number of recommendations for the improved handling of refugee programmes.

Prof. HANS HOFF (Austria), president of the Federation for 1958–59, gave an address on Home and Identity, in which he spoke of the importance of landscape, history, and past experience on the future happiness of migrants, and the need to take account of these factors and apply them scientifically.

Past and Future

The first Dr. Mary Hemingway Rees memorial lecture was given by Dr. H. V. DICKS (London), on Mental Health in the Light of Ancient Wisdom. All the great ancient religions, he said, want man to be happy, good, and free, and they all agree on the threefold need for adjustment, self-realisation, and integration. This is part of the aspiration of mental-health work.

At the general session, Dr. J. R. REES, director of the Federation, outlined some of the plans for an intensive programme of international work for the World Mental Health Year, with five main themes:

1. The needs of children (the family in a changing world).
2. National surveys in the field of mental health and ill-health.
3. Teaching about mental health (professional people and other workers).
4. Mental health aspects of industrial change (human relations in industry).
5. Psychological aspects of migration.

EUROPEAN LEAGUE FOR MENTAL HEALTH

ON Aug. 23 the European League met in Vienna under the presidency of Prof. HANS HOFF.

The Older Worker and Retirement

Dr. DORIS ODLUM (London), immediate past president, opened a discussion on mental health problems of the older worker and of retirement. She pointed out that nowadays more people retain much of their vigour and working capacity until the late 60s or even later, but on the other hand many people even in the 50s cannot get suitable employment and some are arbitrarily retired long before their capacity for efficient work has diminished. The result is not only a serious loss of man-power but also, often, considerable disturbance of mental health.

Few people give up work voluntarily merely because they want more leisure: in fact, many dread the prospect of idleness; they feel discarded and lose their incentive, which can lead to premature deterioration. Unlike older women with homes and husbands and perhaps grandchildren to care for, the retired man may not be wanted in the home or indeed anywhere. In the case of widows, or widowers, or the unmarried, loneliness is often one of the greatest problems.

The preventive and remedial measures which Dr. Odlum discussed include the provision of more suitable work, part-time work, and the avoidance of compulsory retirement as far as possible. Employers, local authorities, and voluntary agencies could do much to prepare people for retirement, to provide activities and interests, and to maintain social contacts. The problems seem to be similar in all industrialised communities and especially in countries which are being rapidly industrialised. The pattern of living is changing too quickly for older people to adapt themselves; also the situation is less favourable to them than that of an agricultural community.

Prof. PAUL REITER (Copenhagen) said that it is now realised that many cases thought to be senile psychoses are really psychogenic and can be greatly helped by medical and social care.

Dr. ANDRÉ REPOND (Switzerland) remarked that the problems of the agricultural communities are considerable and not to be ignored. Their pattern of life, too, is changing. He wondered whether the old *are* unhappy. Have we any real knowledge? If they are, what is the basis of their unhappiness? Perhaps it relates rather to their earlier frustrations and emotional conflicts than to the present.

Dr. CLAUDE VEIL (France) pointed out that preparation for ageing really begins in childhood and at school. The lower the standard of education and cultural background, the earlier the decline of mental powers. He agreed that men would benefit from learning household arts and activities as children. Some people seem never to be at the right age: it is either "you are too young", or "you are too old".

Dr. SOEKEN (West Berlin) said that people who have a religious background or a feeling of purpose adapt much more happily to increasing age.

ISRAEL MEDICAL ASSOCIATION

THE fourth World Assembly of the Israel Medical Association was held in Tel Aviv on Aug. 12–24. The assembly is now a triennial event; and this year it coincided with the celebration of the tenth anniversary of the State of Israel.

Prof. HERMAN ZONDEK, honorary chairman of the conference, remarked that scientific thought had been largely dominated by the mechanistic doctrine of causality; but, despite much progress, the riddle of life had not been solved. The physician in our time was called on to take a greater part in public life than hitherto, particularly in his contribution to education. "The younger generation, drunk with the progress of technology, looks upon an empty soulless world. Humanity in our time is sick, suffering from numerous endogenous ailments of moral, political, and economic kinds, and from extraneous threats to its very existence, the most dangerous of them the unchaining of atomic power. Humanity will with difficulty get rid of this threat; it seems easy to die with the atomic bomb, but how shall we live with it?"

Public Health

Dr. S. BTESH, director-general of the Israeli Ministry of Health, said that the health of the Jewish population of Palestine in 1948 was fairly good. With immigration were introduced many carriers of disease and susceptible persons. The lower standard of living, the lack of proper housing, and the ignorance of the immigrants in matters of hygiene resulted in deterioration of the health of the people, culminating in an increase in infant-mortality and crude death-rate, and in the spread of tuberculosis, poliomyelitis, and malaria.

Intensive health measures had resulted in effective control of most of these conditions, and at the end of the ten-year period the health conditions of the country compared favourably with those in the U.S.A. and most European countries.

There was 1 doctor to about 450 inhabitants, and there were about 3 general-hospital beds to 1000 inhabitants.

Prof. G. G. MER said that malaria in Israel is dying out. The present low incidence had been accomplished by control of anopheles breeding, the use of residual insecticides, and efficient medical services. The occurrence of a few scattered cases pointed to the presence of human carriers in the country. Because in the neighbouring countries, too, intensive anti-malaria work was being carried out, the complete eradication of malaria in Israel could be regarded as a certainty, provided immigration of malaria carriers could be prevented and the present number of carriers could be reduced.

Serum-lipids

DR. D. BRUNER said that the population was now composed of, on the one hand, European Jews, among whom there was a high incidence of coronary-artery disease in middle age, and, on the other hand, Yemenite Jews, who were practically free from atherosclerotic heart-disease in middle age. Of 32 Yemenite farmers who had been investigated, none had had a level of β-cholesterol over 180 mg. per 100 ml.; and 27% of the total cholesterol was bound to the α-globulins. In this group the percentage of α-cholesterol was nearly double that in a group of patients with ischæmic heart-disease and a third higher than that in healthy European Jews.

Mediterranean Fever

Dr. H. HELLER, Dr. E. SOHAR, and Dr. L. SHERF reported that the great majority of patients with familial Mediterranean fever were non-European Jews, and the second large group consisted of Armenians. The disease began in childhood or early adolescence and persisted for many years. It was characterised by recurrent attacks of fever accompanied by abdominal pain, arthralgia, chest pain, and sometimes skin manifestations. The attacks were brief, usually lasting for twelve to forty-eight hours, and recurred at irregular intervals. During the abdominal attacks signs of peritoneal irritation usually appeared. In X-rays of the abdomen fluid levels were found in the intestinal loops. A small transient pleural effusion might be detected in chest films. Joint pains might be restricted to one joint or might attack several at a time; sometimes the affected joint was warm, red, and swollen, and fluid might be found in the synovial sac; joint manifestations usually declined more slowly than the others. Between the attacks the patients were well. The disease terminated, in some cases, in renal failure and death due to amyloidosis. Extensive laboratory investigations had revealed very high erythrocyte-sedimentation rates, high fibrinogen levels, and slight spherocytosis. In many cases proteinuria was found as well. Therapeutic measures were of no avail. No patient ever recovered, but remissions did occur. During pregnancy complete remission was usual. The clinical picture, as well as the familial incidence and the limitation of the disease to certain ethnic groups, suggested that the cause was an inborn error of metabolism.

Pneumoconiosis

Dr. E. E. LIEBER (Great Britain) described an inquiry into whether the dust and vapours from various chemical substances could cause chest disease. He pointed out the importance of medical and radiographic examination of affected persons and of skin-sensitivity tests. The substances involved included (a) dusts (such as glass monofilaments from the cutting and handling of mats, cloths, rovings, and beryllium-copper alloy, fine-glass and epoxy-resin dust, and polyester dust) and (b) vapours (styrene from resin compounding and mixing, and methylethylketone peroxide accelerator). In some patients who came under his care there was a reduction in vital capacity, and chest radiographs showed occasional lung markings and sometimes emphysema. The prognosis in all cases was excellent. The patient's condition did not continue to deteriorate after removal from exposure, and this dust disease might be described as a "benign pneumoconiosis". Dust-extraction equipment and the usual additional prophylactic measures protected workers engaged in handling glass fibres and epoxy resins.

Dehydration

Dr. M. TOOR said that workers in the Dead Sea region in the summer drank 5·5–10 litres a day. Despite this intake, outdoor workers showed signs of dehydration, manifested by weight loss, hypernatræmia, slight metabolic acidosis, and relative hyperchloruria. The daily urinary output was in some as low as 300 ml. Hyperventilation, present at rest, increased after work. The sodium-potassium ratio in the saliva decreased after work. In order to determine the influence of varying water intake, 10 fully acclimatised subjects had been examined after they had walked for two hours at 6 km. per hour. The outdoor temperature was 42°C. They were divided into three groups: (*a*) without fluid intake; (*b*) without limitation of fluid intake; (*c*) with forced fluid intake. The group without fluid intake had shown an average rise in body temperature of 1·9°C and an average drop in body-weight of 1225 g. per hour. The glomerular filtration-rate was low and little urine was excreted; the alkali reserve remained unchanged, but the pH dropped slightly. The group which drank according to inclination lost 400 g. body-weight per hour, and the average body-temperature increased by 0·7°C. The group with forced water intake drank nearly 2 litres per hour and gained 500 g. per hour in weight; body temperature remained constant. Their perspiration did not increase in direct ratio to the water intake; but the glomerular filtration-rate, the amount of urine, and the urinary sodium increased. The alkali reserve dropped, but blood pH did not change. This experiment indicated that fluid intake according to thirst urge was not sufficient; on the other hand, positive water balance could prevent disturbances in homœostasis even in the hot climate of the Dead Sea region.

Before Our Time

ALFRED RUSSEL WALLACE
(1823-1913)

AT school I was given as a prize Wallace's *Travels on the Amazon and Rio Negro*. I remember being puzzled when I read on the title-page the author's claim to be the co-discoverer with Darwin of the theory of the Origin of Species. I had heard a great deal about Darwin but Wallace's name was new to me. Many people must have been equally puzzled on reading the centenary articles which have recently appeared; for most of these, while starting off with the presentation of the two independent papers by Darwin and by Wallace to the Linnean Society on July 1, 1858, thereafter refer only to Darwinism. Some account of Wallace and his relationship with Darwinism may therefore not be out of place.

Alfred Russel Wallace was born at Usk, Monmouthshire, his father being nominally a solicitor but actually a lifelong idler. Leaving school at the age of 16 he became a land surveyor and architect and later a schoolmaster. He early became interested in botany, and a chance meeting with H. W. Bates extended his interest to entomology and in due course led him to spend four years on the Amazon (1848–52). On the voyage home the ship was completely destroyed by fire and most of his collection was lost. In 1854 he went to Malaya, where he spent eight years in exploration and in pondering over the problem of evolution. In the idea of evolution itself there was nothing new. It had been adumbrated by Goethe (some people find suggestions of it in Empedocles and Ovid) and developed by Lamarck, and it was now engaging the attention of many thinkers, among them Herbert Spencer, Robert Chambers, and Sir Charles Lyell. The unsolved problem was the cause of evolution.

In February, 1858, while recovering from an attack of ague at Ternate in the Moluccas, Wallace suddenly recollected Malthus's *Essay on Population* which he had read twelve years previously and he at once realised that this gave him the key which he sought. "There suddenly flashed upon me," he wrote, "the *idea* of the survival of the fittest." He hurriedly wrote out his theory and sent it to Darwin. Darwin, also inspired by Malthus, had for many years been accumulating evidence on similar lines. Lyell, evidently realising from his wider experience that a fundamental generalisation was imminent, had been urging him to publish his results lest he be forestalled. Darwin, however, was in no hurry.

On receiving Wallace's communication (the author being unknown to him) Darwin was dumbfounded. "I never saw a more striking coincidence," he wrote to Lyell. "If Wallace had my MS. sketch written out in 1842, he could not have made a better short abstract. Even his terms now stand as the heads of my chapters." On the advice of Lyell and Sir Joseph Hooker, Wallace's essay and an abstract of Darwin's conclusions were jointly read. Though they were in general agreement, the views differed in certain respects. In particular, Wallace early abandoned the Lamarckian doctrine of the inheritance of acquired characters, but Darwin adhered to it for the whole of his life, putting forward his complicated pangenesis theory in explanation.

The simultaneous appearance from two sources of a revelation which shook the scientific and religious worlds might well have had unpleasant consequences. But the very reverse happened. So far from indulging in jealousy and acrimony, Darwin and Wallace became lifelong friends with the warmest mutual regard. On the authorship of the theory they vied with each other in deference. "You ought not," wrote Darwin, "to speak of the theory as mine; it is just as much yours as mine." To this Wallace replied: "As to the theory of natural selection itself I shall always maintain it to be actually yours and yours only." This he certainly did, for in all his writings he called the theory "Darwinism".

On his return from Malaya Wallace began to write voluminously. The most important of his biological books are *The Malay Archipelago*, *The Geographical Distribution of Animals* (which became a standard work), *Tropical Nature*, *Australasia*, and *Island Life*. In *The Wonderful Century* he displays his interest in physics, chemistry, astronomy, geology, and cosmology.

Unlike Darwin, who confined his activities to science, Wallace was interested in everything that concerned human welfare.

At an early age he was attracted to Robert Owen's New Lanark experiment and later he was influenced by Herbert Spencer's *Social Statics*. After many years' hesitation he became a socialist, numbering among his friends the leading socialists of the day. He trenchantly poured out his views on capitalism, wages, poverty, and militarism. To the emancipation of women he attached a peculiar biological significance, linking it up with the theory of natural selection. He was convinced that if women became economically and socially independent they would select their mates with more discretion, so that "numbers of the worst men among all classes who now readily obtain wives *will be almost universally rejected*". He summarised his sociological views in *The Revolt of Democracy* and *Social Environment and Moral Progress*, both written in his 90th year.

His special interest, however, was the nationalisation of land, a subject on which he felt that his early experience as a surveyor enabled him to speak with authority. When, in 1881, as the result of an article which he had written in *The Contemporary Review*, the Land Nationalisation Society was formed he became its president and he retained the post until his death.

Like so many intellectuals he was singularly naïve in medical matters.

In *My Life* he relates how he was cured of asthma by living almost entirely on beef with small quantities of bread or vegetables, fruit, eggs, and light milk puddings. This regimen he learnt through a friend from an American doctor named Salisbury who claimed to have proved that asthma, palpitations, gout, rheumatism, and other disorders were due to malnutrition caused by interference with digestion and assimilation through the excessive consumption of starch. Wallace lapped all this up. "Dr. Salisbury", he wrote, "has found for the first time in the history of medicine, a *cure*—not merely a *palliation*—for these painful and distressing maladies." He did not, however, propagate this opinion.

More important is his violent opposition to vaccination. In *Forty-five Years of Registration Statistics* and again in *The Wonderful Century* he claims to prove from the Registrar General's figures and other sources that vaccination, so far from preventing smallpox, actually increased susceptibility to it. It was "a gross interference with personal liberty and the sanctity of the home. It was utterly opposed to the teaching of sanitary science and one of those terrible blunders which, in their far-reaching evil consequences, are worse than the greatest of crimes."

While he was a schoolmaster he became interested in mesmerism, phrenology, and phreno-mesmerism, the last-named being a procedure whereby certain " faculties " were elicited in the mesmerised person by touching with the finger the part of his head indicated by phrenological teaching. From this Wallace was led to spiritualism of which he became one of the most prominent advocates, regarding it as the greatest discovery of the century, surpassing even his own discovery of natural selection.

In *Miracles and Modern Spiritualism* he gives a detailed account of the phenomena including those which he himself witnessed in this country and America. Spiritualism was, in his opinion, superior to revealed religion. " After death man's spirit survives in an ethereal body, gifted with new powers, but mentally and morally the same individual as when clothed in flesh." He enters upon an endless progression, the rapidity of which depends upon the extent to which he used his faculties while on earth. Spiritualism thus provided a stimulus to moral behaviour during terrestrial existence. Wallace was always careful to describe the phenomena as " preternatural " rather than " supernatural ". His friends might scoff, but at least he was in the good company of Sir William Crookes and Sir Oliver Lodge.

Financially, Wallace fell on evil days. His income from his numerous books and lectures was surprisingly small and was reduced by injudicious investments and by the defalcation of a builder. But this was not the worst. In 1870 he accepted a wager by a certain John Hampden to prove that the surface of inland water was curved. The experiment took place on the Bedford Level in the Fens, with the editor of *The Field* as arbiter and stakeholder. Though Wallace was pronounced the winner his adversary, despite his felicitous name, defaulted, taking advantage of a legal quibble and making himself a bankrupt. Unsubdued, moreover, by four prosecutions for libel and a term of imprisonment Hampden persecuted poor Wallace with the most scurrilous abuse for fifteen years. Legal costs and the expense of the experiment reduced Wallace's finances to the lowest ebb. In 1881, Darwin and Huxley persuaded Mr. Gladstone to grant him a Civil List pension of £200 a year. He died in his 91st year, his mind and pen active to the last. Among the honours he received were the Order of Merit, the Royal medal and the first Darwin medal of the Royal Society, the hon. LL.D. of Dublin University, and the hon. D.C.L. of Oxford University.

Fearless and uncompromising, Wallace never minced his words. The Joint-Stock Companies, he declared, swindled and plundered the public, the whole commercial fabric of the country was permeated with dishonesty, gambling, and robbery, while the administration of justice was thoroughly immoral. He castigated scientific orthodoxy and was never so happy as when propounding or defending an unpopular thesis. As may be imagined, his critical faculty often deserted him and he lacked a sense of proportion. He was, for instance, ready to believe that spiritualists in the United States numbered 8–11 million, not stopping to reflect that this meant more than half the then existing adult population. Though he did not believe in Christianity he was a confirmed deist. He held that life could be explained only by postulating a Life Principle which implied a Creative Power, a Directive Mind, and an Ultimate Purpose which was the Development of Man, " the one crowning product of the whole cosmic process of development ".

FFRANGCON ROBERTS.

In England Now

A Running Commentary by Peripatetic Correspondents

My work is full of meaning—or at least I mean it to be. The only trouble is that I just can't see what it means. Hints in plenty: oh yes! But I can't get the meaning of them. *Pro*meanings: that's what they are; they only need activating. Perhaps that's the trouble; my brain is deficient in promeaning*ase*: it won't activate. Or, half a minute: it might be worse; suppose it's not just a deficiency state: perhaps it's a toxic condition; perhaps my mind actively secretes an *anti*-promeaningase. How to neutralise this? Can it be bound to plasma-protein and taken to the liver for detoxication? *Degrado*antipromeaningase? What's that? Needs a co-factor? *co*-degradoantipromeaningase? Now we're getting somewhere: I can almost see what it means . . .

No! the pattern's lost again. The nascent meaning showed a strong selective affinity for *anti*-meaning which converted it rapidly to inactive *meta*-meaning. But that's what it all means! Promeaningase and anti-meaning are clearly in excess and therefore constant; so that we have a system of effective first-order consecutive reactions

promeaning→meaning→metameaning

and—oh but look: how ghastly! This means that meaning has only a fleeting ephemeral existence after all. I really do call that pretty mean, don't you?

• • •

Drinka Pinta Milka Day? You'll be lucky. Our village has been shaken from taproom to shippon. Joe Moffat has been booked for obstructing the highway. Not, mark you, with the old green van that has the mudguards tied with binder twine, not even with the shiny new tractor. We could have forgiven the Law for that: Joe spends a lot of time in the Plough on market day. No, it was far worse, he was run in for blocking the road with his milk cows. It would never have happened in the old days: P.C. Grimble would have got off his bike and helped to turn the herd in at the gate. But not those new motor patrol chaps from the town: they focused their radar on the backside of Buttercup and timed how long she took for two furlongs. Joe got fined a pound and had to listen to a sermon on how to fit sixteen cows into the *Highway Code*.

I feel very heavy-hearted about the whole affair. The rolling English milk cow made the rolling English road. There is some elemental simplicity about waiting for cows to move on. Quite a different mood from fretting behind 100 tons of steel boiler or a surrealist aircraft fuselage on the trunk road. All our motorists are fully conditioned to lowing herds winding slowly o'er the lea, even if they are not quite sure what is a lea. It would be vulgar impatience to expect a cow to trot single-mindedly from grazing ground to milking parlour, and it would cost a lot more from the public purse to mow the grass verges. No, there is something very soothing in slipping the clutch gently behind a herd of cows. Those extraordinary pelvic bones protrude like the tail fins of a modern car: how curiously pudendal have become the rear lights of Luton. One could muse on about following cows and cars, keeping a decent interval from the one in front. But cars go on like that for hours all the way to Brighton: ten minutes and two furlongs can pass a lot of cows.

Of course, Joe knows my car. If he thinks I ought to be off to an urgent case, he turns the herd with the dog, but that is not often. Most days he just jogs alongside the open window, talking of life and country things, and poking incredibly unhygienic fingers into his mouth to whistle commands to Moss. The herd really do not need a cow dog: they have strolled the road for years. And when they have turned in off the tarmac, Joe and I lean over the top bar of the gate and put the world aright. Alas, those happy days seem gone. A resolute tractor-mounted Moffat will have to punch his cows in the derestricted stampede of death on our roads. Sixteen udders will sway in the churning rush, sixteen cuds will turn sour.

All that will be left for us to say to you will be: Eata Nounca Cheesa Day.

• • •

Each year at this season our city undergoes the ordeal of a festival of music and drama, and the hounds of culture can be heard baying in every close and wynd of the Old Town. But it is refreshing to be reminded that culture is not a prerogative of any particular income-group or intellectual coterie.

Yesterday I had to decline the offer of a game of golf with a senior colleague (a celebrated physician) because I was going to *Tristan and Isolde*. He was aghast: "What! Pay £2 and sit for five hours listening to all these Germans screaming away?"

This morning, at an autopsy on one of my patients, the mortuary porter kindly inquired if I had enjoyed *Tristan*, and added: "I've seen it twice; Wagner is very good, but give me Verdi every time."

• • •

On the coach on the way back I happened to be sitting next to him. His eyes were still alight with the fire of battle. "We will have them at the hospital," he said. We had been on our annual trip to the sea and our Administrator had spent the whole time on the dodgems. With his usual single-mindedness and determination, he had hurled his car against all comers; with dexterity and speed he had bashed and rocketed all other cars off their course. "The hospital will run on wheels," he exclaimed. "We will have them in the corridors and have dodgem parks outside each ward, at the front door, and all centres of activity. We shall have to ban all pedestrians. You can each have your own car," he continued generously. "We will give Matron and the sisters one each. We will have dodgem cars, dodgem stretchers and dodgem wagons for the stores. They won't be noisy, all electric, fixed with silencers. It will be quieter than it is at present. Of course we will have to have one-way traffic so there will be no bumping," he continued regretfully. "We might have an occasional Bump Day though," he added musingly. "Think of the time it will save. No more walking through miles of corridors." I imagined the Chief's round hurtling off from the front door to the back block and groaned to myself. "It will all stop at the ward doors," he said. "Of course, we shall have to cut them out on visiting days," he pondered, "the patients see little enough of their visitors already with television being on . . ." I didn't listen any more. He was still talking rapidly. I fell asleep.

I think he really means to go through with it. Workmen have appeared in the corridors and a wire mesh is beginning to cover the ceilings.

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Sophistication in the treatment of myocardial infarction is unbounded. After three days of frightening arrhythmias, electrolyte manipulation, and norepinephrine, my friend was well enough to state his own ideas on treatment. "Not by electrolytes alone" was his philosophy. So his wife and I, and a most enlightened hospital administration, have prevailed on a well-known string quartet in this mid-Western city to play for him. Every afternoon they trundle in, and they are at present wading through the Beethoven quartets. We persuaded them that atonal music might play havoc with his rhythm.

My friend's room is a very popular place these days. And his heart? Beating away in perfect time.

• • •

In that part of Yorkshire which will eventually comprise the South Riding it is an ignoramus indeed who is not aware of the St. Leger and of Race Week. At this time "failed attendances" in the outpatient departments may approach 50% of the total appointments, and those who do attend are in their Sunday best and apologise for troubling the doctor at such a time. Non-racing newcomers who fail to make note of this *jour de fête* may sooner or later find themselves at a disadvantage in the surgery: for in later months medical histories will include perhaps a cough which began "happen the month before race-week" or a pain which was previously experienced "the year Lupus came in first."

Letters to the Editor

EDUCATION FOR THE TROPICS

SIR,—I hope there will be a burst of applause, from spectators and players alike, for Mr. Wright's plea (Aug. 30) that education should take account of medicine in the tropics: a crescendo of delighted drumming would be more appropriate than polite handclaps from the pavilion.

In East Africa, to continue Mr. Wright's sporting simile, the game is much the same as in West Africa, though the pitch may be a little different. My strongest recollection is of rural dispensaries, of which in Uganda there are about 10 for every hospital, where the game may be at its simplest but the players are just as much in earnest. Here attends a third of the population annually,[1] and probably nearly *every* baby in its first year,[2] all to be seen by locally trained medical auxiliaries: there may be a small ward with a few beds, and the most powerful weapon is penicillin.

Common sense suggests that the rules of this game also should be taught—how to integrate these rural units with the hospital service, how best to make use of the times the doctor can visit them, what part they can play in prevention of disease, how much can be expected from the medical auxiliaries. Examples showing how other underdoctored countries have made use of such institutions would prepare students for this aspect of medicine in the tropics.

The educational, the social, and the preventive aspects of medicine are, as Mr. Wright so clearly argues, all-important in areas where there is so little background of health education, societies are so different from English, and successful prevention can reap such encouraging rewards. It is in these fields that physical *example* can play such a large part. To take a bad example, it is our own emphasis on "the microscope, the pill, and the injection" that has evoked such a demand for them from the local populations; and now the demand is often used as an argument for persisting with this disastrous imbalance (in Uganda, overall mortality under 14 years of age is 400 per 1000 [3]). Another bad example has followed where no good example has been given: mothers are aware of the dangers of malnutrition, and therefore buy the imported baby-foods on which Europeans feed their children; but they can neither read the instructions nor afford enough—with the tragic result that malnutrition is aggravated. An encouraging response has followed the example afforded by a gift of skim milk powder from the Church World Service of the U.S.A.: in the child-welfare clinics where this has been given away, attendance has doubled in the past two months. If the experience of other countries is repeated, the knowledge of the benefits of good nutrition will remain even when the gift has come to an end: the misfortune is that there are only a score or so regular child-welfare clinics in Uganda at present—although there are about 900,000 children under 5 years of age.

One point to which I think Mr. Wright might have drawn more attention is that in the tropics the majority of doctors—certainly most of those associated with the kind of medicine he describes—are in the Government service. Now it is a strange paradox that under these conditions the fewer the doctors the less medicine (either preventive or curative) they seem to practise. Although surrounded by a fascinating variety of medical conditions, and in their monthly records accumulating figures of the greatest value for a public-health policy, the only figures which many are allowed to take an interest in are those of numbers of blankets or amounts on payrolls. In tropical Parkinsonism, office work expands to the exclusion of medicine.

Mr. Wright calls for "rural medical officers equipped with the necessary imagination and energy" and feels

1. Report of the Medical Department of Uganda for the year 1956. Entebbe.
2. Based on monthly returns from rural dispensaries, 1956.
3. Martin, C. J. *Population Studies*, 1953, 7, 181.

that the "centralised administration" has little part to play; and on this premise he builds his hopes for the value of better education for those going to the tropics. But in fact the administration has an all-important part to play. Medical officers, like other human beings, tend to concentrate on what their superiors show an interest in: if the director puts foremost the many aspects of medicine in the tropics, the M.O. will do likewise; if he puts foremost accounting, storekeeping, and administration, so will the M.O. The problem is how to ensure that the directors have the right outlook; and this, I feel, is beyond the scope of education.

London, W.C.1. JOHN MCFIE.

BREAKING UP THE MENTAL HOSPITAL

SIR,—While applauding Dr. Baker's application of methods of combating institutionalisation, I think that several of his propositions (Aug. 2) require scrutiny.

Banstead Hospital, he says, now has 450 patients less than three years ago. Most mental hospitals have about 10% of their population on leave at any time, and if it were decided to discharge patients instead of sending them on leave their population would drop; but this is not necessarily a good thing. Dr. Baker does not tell us how many of the discharged patients have found their way into other mental hospitals or have committed suicide.

Banstead has a catchment area which includes parts of Westminster, Chelsea, and Battersea; the population is mobile, and it is reasonable to suppose that more discharged patients would move out of the area than into it. Furthermore several other hospitals take patients from the catchment area of Banstead, and some doctors would prefer to send patients to these because they do not agree that a voluntary patient should be required, *before admission*, to sign a form giving permission for electroconvulsion therapy, insulin, and any other treatment considered necessary.

The 40% rise in admissions given may include readmissions. It is not clear to me whether in the past many of these "admissions" would have returned to hospital during a period of leave.

Apart from the possible speciousness of statistics, a very important question arises if one looks at the effect of rapid discharge on the patient and community. Has investigation been made of the distress caused to the patient, his family, and others? Can Dr. Baker reassure me that in breaking up the mental hospital he is not breaking up the home? I wholeheartedly agree that businesslike methods are desirable in mental hospitals; but, whereas a business man takes the consequences of his decisions, the psychiatrist makes decisions which do not affect him: it is the patient and his family who take the consequences. There is a danger that the public may be made less tolerant to mental disease by having it thrust among them before adequate aftercare services are provided; and this in turn may hamper the development of these services.

I think it is generally agreed that a neurosis characterised by apathy, submissiveness, and loss of individuality results from factors arising in an institution. It is only in the past few years that this neurosis has been realised to have an ætiology separate from the mental disorder causing admission.[1] From visits to other hospitals and reading, it is my impression that many hospitals have introduced, and are introducing, programmes to stop causing this disorder and to cure it where it has been produced. Dr. Baker may think that dividing a large hospital into smaller units is a solution, but when examining this contention one should remember that hospitals built on the villa system with units of 30–50 patients also produced institutional neurosis in quantity and degree much the same as the hospitals with "barn-like wards" built in the Victorian era.

To say that the provision of hostel accommodation and sheltered workshops is not the proper function of a mental hospital seems to me a verbal quibble. One has has only to read Dr. Houston's imaginative article, A Project for a Mental Health[2] Village Settlement,[2] and Professor McKeown's Balanced Hospital Community[3] to realise the possibilities of the future. I cannot see that mental hospitals can contract out of making such provisions.

Is it sufficient to treat the patient of today as the neighbour of tomorrow? Should we not aim at treating patients as we would like to be treated ourselves?

Shenley Hospital, near St. Albans, Hertfordshire. RUSSELL BARTON.

ULCERATIVE COLITIS

SIR,—We are grateful to Dr. Balfour Sclare (Aug. 9) for suggesting that the questionnaire in our paper of July 19 should have been given in detail. It was omitted to save space, but we would gladly forward a copy to anyone who cares to see it. The patients surveyed do not, of course, represent a "fair cross-section" of all cases suffering from ulcerative colitis: as they were all sufficiently ill to require an ileostomy, milder cases must have been excluded. However, we could say with certainty that every patient did suffer from the disease—which in a more comprehensive series could not be guaranteed. We are pleased that Dr. Sclare agrees with us on our proposed prospective inquiry on a longitudinal basis, but it is of interest that the present questionnaire method has already yielded information which is very close to that of the more detailed long-term studies of Engel. One of us (M. S.) had the opportunity of visiting Professor Engel in his clinic at Rochester, N.Y., after our paper was submitted, and a reconciliation of our statistics revealed many points of similarity: differences originally apparent were due to the methods of presentation.

We can understand the reactions of Dr. Ranyard West (Aug. 9) and Dr. Paulley (Aug. 23) to our inquiry. Most psychotherapists working with patients with ulcerative colitis are quite convinced of the psychological processes "that are causally connected with the symptoms in sufferers from this disease"; yet the theories of these psychological processes are many and some are mutually exclusive. We shall not burden your readers with more references, but suggest again that they consult the papers of Engel which we have quoted. A psychosomatic hypothesis should fit in with the essential organic features of the disease and its natural history, and our *preliminary* inquiry into the order of appearance of symptoms in a very large (if not the largest) group of patients with proven ulcerative colitis does not encourage us to accept the existing hypotheses, but to study them even more critically.

We agree that psychotherapy in some patients is of value, but that does not support or prove the seven or eight psychosomatic hypotheses on the ætiology of the disease or tell us which is the most valid. Our paper (a joint effort by psychiatrist and surgeon) was not designed to prove that the condition was not due to psychological happenings. We are not prepared to accept the conviction of others—sometimes based on as few as two or three patients—unless they can be supported by proper

1. Martin, D. V. *Lancet*, 1955, ii, 1188.

2. Houston, F. *ibid.* p. 1133.
3. McKeown, T. *ibid.* 1958, i, 701.

evidence. We do not claim infallibility for our preliminary inquiry, but in reply to Dr. Paulley's arguments against it we can only repeat "the value of the present method cannot be adequately tested by argument, but only by a carefully controlled prospective inquiry, which we propose to do".

The Queen Elizabeth Hospital, Birmingham, 15. M. SIM
B. N. BROOKE.

UNIDENTIFIED DRUGS

SIR,—Patients often come to hospital with tablets which their general practitioners have been giving them for a long time, and the name of which they do not know. The houseman has to find out the name of the drug, and this often results in delay in treatment.

Would it not be better if the general practitioner told the hospital of any chronic illness in a patient referred for some acute condition, and the treatment that is being given? This would be a great help for the inexperienced junior members of the hospital staff, like myself.

St. Albans City Hospital, St. Albans, Hertfordshire. BISWARUP BHATTACHARYA.

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—Your annotation,[1] combined with Mr. Charnley's comments (July 5), has reminded me that we lack a basic philosophy which might illuminate our search for the cause of pain. The pathology of pain is ill-understood but accepted in general as pressure; therefore he who first propounds a plausible theory of pressure wins the honours.

But let us examine Mr. Charnley's invention of a suddenly expanded disc causing pressure like that in an abscess.

This is the ghost of turgor again; and I thought that that had been laid fourteen years ago. Self-expansibility, said Ffrangcon Roberts,[2] is a quality unknown in physics: "to ascribe turgor or power of expansion to the nucleus is to invoke some property quite unknown in the physical world and takes Medicine back to the obscurantism of the Middle Ages".

Instead of turgor, Mr. Charnley calls it hydrophilia; dried discs swell when placed in water. Of course they do, as does any piece of dead cartilage. The disc is nothing but a resilient bit of fibrocartilage, more cartilaginous at its centre and more fibrous at its margin. Nucleus pulposus and annulus fibrosus are verbal expressions and not entities. Like other cartilaginous structures the disc cushions sudden or intermittent pressure by flattening, and it is restored to its previous shape when the compressing force is removed. Its resilience is shown by the rarity of disc lesions in compression fractures of the vertebral bodies.

Like other cartilage, the disc cannot have a weight-bearing function; continuous pressure causes its absorption or degeneration. The weight-bearing structures in the back are the pedicles and articular processes; narrowing of an intervertebral disc is always secondary to failure of these structures through decalcification.[3] Narrowing of the space, therefore, is not the cause of the pain but a later effect of the decalcifying process.

I am glad to read: (1) that Mr. Charnley has never seen the acutely swollen discs; (2) that protrusions are rare in acute lumbago; (3) that pain in acute lumbago is not proportional to the change in the disc. Could this not possibly mean that the disc is not the cause of the pain—that the pain, as elsewhere, arises in muscular, synovial, or ligamentous structures?

Melbourne. MICHAEL KELLY.

1. *Lancet*, 1958, i, 1214.
2. Roberts, F. *Brit. J. Radiol.* 1944, **17**, 54.
3. Roberts, R. A. Chronic Structural Low Backache. London, 1947.

LEARNING TO LEARN

SIR,—The Students' Guide (Aug. 30) outlines present-day medical education in your usual lively manner. Especially interesting is your treatment of the faculty of learning. Teachers, absorbed in planning curricula, overlook that even more important than the science of teaching is this art of learning. Not all of us have to instruct, but we all need to assimilate, and we painfully rediscover what Hippocrates told us—that in a brief lifetime it takes a long while to learn. We get less from regular teachers than from irregular sources. How can we best acquire a habit of receptivity to unconventional means of knowledge? Of course, each of us must work out his private technique.

Learning does not deal with external knowledge alone: we have to revalue our own capacity for handling experience. In the past, many doctors changed over to a line of medicine different from that in which they began. What this means is that they fathomed their own inclinations later than the average. General practitioners sometimes became successful consultants, for the best of all reasons—they found that people wished to consult them. A young doctor today is not encouraged to change his course, but for any individual the start of true learning may be the moment he realises he had taken a wrong direction. Some advice from late beginners, who found a vocation through their own efforts and not from teachers, would be illuminating next year.

London, W.C.1. HARLEY WILLIAMS.

GLUTETHIMIDE POISONING

SIR,—A patient with glutethimide poisoning has previously been reported from this hospital by one of us.[1] It was noted at that time that respiratory depression was very slight, that the condition responded to the administration of bemegride and amiphenazole, and that the patient, during the period of coma, had attacks of carpopedal spasm closely resembling tetany. These attacks were exacerbated by the administration of bemegride. We have recently seen the identical features in another patient with glutethimide poisoning.

A married woman, aged 39, who had a long history of depression, was admitted to the Royal Victoria Infirmary on July 30, 1958, in deep coma. Three and a half hours before admission she had taken 22 tablets (5·5 g.) of glutethimide ('Doriden'). Her pupils were of normal size and failed to react to light, and the corneal reflexes were absent. The tendon jerks were depressed and the plantar responses were flexor. Respiration was not markedly depressed. Gastric lavage was performed and bemegride administered as a continuous intravenous infusion; in all, 850 mg. was given in two hours. The limb reflexes returned within thirty-five minutes and the pupil reflexes within three hours of starting bemegride.

Soon after admission transient attacks of spasm of the limbs, associated with tetanic spasm of the hands, were noticed. Trousseau's and Chvostek's signs were negative, the serum calcium and phosphorus were normal, and intravenous calcium gluconate was without effect. Bemegride increased the spasms. The patient also had intermittent head retraction, and attacks of laryngeal spasm. The muscles in spasm changed frequently, both flexor and extensor groups being involved intermittently and quite independently in all four limbs. This resulted in an appearance in the upper limbs sometimes simulating tetany and sometimes a posture reminiscent of Erb's palsy. The attacks of spasm decreased in severity and disappeared within fourteen hours.

The clinical features of this case were so similar to those of the previous one that we feel that there is no doubt

1. Rowell, N. R. *Lancet*, 1957, i, 407.

that the attacks of muscle spasm were due to glutethimide. The site of action remains obscure, but, in view of the changing posture of the limbs, this may be in the corpus striatum.

This case underlines the safety of the therapeutic dose of glutethimide, and also that it is a suitable sedative for patients where respiratory depression should be avoided. Bemegride is indicated in cases of poisoning.

A. R. HORLER
Royal Victoria Infirmary, Newcastle upon Tyne, 1. N. R. ROWELL.

MIDGET ANÆSTHETIC MACHINES

SIR,—With reference to Dr. Burton's letter last week, the universal adoption of the B.S.I. pin index fitting for medical gas cylinders should facilitate the development of lightweight anæsthetic machines.

We have had in use for six months an apparatus weighing 7 lb. that can be fitted with any size of pin index cylinders. The basis of the apparatus is combined cylinder yokes, regulators, and plastic flowmeters for the gases. The fittings are standard anæsthetic equipment so that additions or replacements are easily available. A full range of gases can be used and any standard vaporising bottle included in the circuit. The similar heads for all sizes of the new cylinders together with the use of lightweight alloys in the machine allow the machine to serve in daily use and as a portable emergency apparatus.

Royal Marsden Hospital, London, S.W.3. J. D. K. BURTON.

THE PLACE OF THE RESEARCH INSTITUTE IN THE ADVANCE OF MEDICINE

SIR,—Sir Charles Harington's article [1] will have been read with great interest by medical research workers everywhere. As his closing theme he mentions the difficulty of establishing sufficient contact between the laboratory research institute and the sick patient, and considers the possible advantages of establishing institutes for clinical research.

Conditions in Malaya are very different from those in England, but this Institute for Medical Research has over a few decades achieved a fortunate blend of laboratory and clinical work.

The Institute itself has no beds, but is situated next to a large general hospital. When a patient is admitted to the hospital with an illness known to be of interest to one of the Institute staff, we are notified, and, if after initial examinations the patient is deemed suitable for further research studies, the hospital physicians have generously allowed us to take over complete control of the patient while retaining the use of the hospital bed. This has been practised in the study of such diseases as beriberi, malaria, filariasis, and the nutritional anæmias.

This happy state depends entirely upon the good will and confidence between the hospital and Institute staff at the personal level—a trust which has been built up for half a century.

Such a system has the great advantage of flexibility, for when the study of any particular problem has been completed it is easy to pass to another by drawing upon a different type of patient in the large hospital pool.

Many of the difficulties in tropical medical research are avoided by this efficient system, which allows maximum information to be gained from the material at hand. Experience here bears out Sir Charles Harington's view that such a combination of clinical and laboratory research can provide valuable results.

Institute for Medical Research, Kuala Lumpur, Malaya. P. W. G. TASKER.

1. *Lancet*, 1958, i, 1345.

FERTILITY AND MENTAL ILLNESS

SIR,—In your leading article of Aug. 16 you refer to a finding that "schizophrenics . . . were as a whole about a quarter as fertile as the general population". It may be of interest to point out that Reiss and Hemphill [1] have shown that in many advanced schizophrenics there is vascular degeneration of the testes; this could undoubtedly have had an effect on the lowered fertility. I have also noted the relation between hypothalamic disturbances and impaired fertility, and many men suffering from such conditions are infertile. In two cases of narcolepsy there was severe infertility, and other observers have already noted this connection. It may well be, therefore, that there is an organic basis to be taken into account as well as the "premorbid schizoid personality" making marriage less likely to which you refer.

Manchester. BERNARD SANDLER.

CARDIAC COMPLICATIONS OF COXSACKIE-VIRUS INFECTION

SIR,—We have already described [2] infection with Coxsackie virus type B4 as a cause of benign pericarditis. Recently another of these cases has shown evidence of infection with Coxsackie virus type B3; and we would like to draw attention to the signs of cardiac involvement.

A man, aged 50, contracted an acute febrile illness which lasted for 5 days. The onset was sudden with shivering, sharp pains in the chest, and considerable dyspnœa. The initial temperature was 102·4°F. There were crepitations over the lower lobe of the right lung, and pericardial friction was audible over the precordium, especially at the base of the heart. The heart rhythm was regular, rate 100 per min. X-ray of the chest on the day of admission showed moderate cardiac enlargement and an area of "ground-glass" consolidation in the lower lobe of the right lung. An electrocardiograph at this time was abnormal; the T waves were negative in leads I, aVL, and V_{1-6}, with slight elevation of the S-T segments. In association with the clinical findings these changes may be regarded as evidence of cardiac involvement with pericarditis. Ten days later the electrocardiograph had reverted to normal, and repeat X-ray of the chest showed that the heart was now normal in size, and the consolidation of the right lung had resolved. Also the patient had made a complete clinical recovery.

Results of neutralisation tests for Coxsackie virus type B in tissue culture (monkey kidney) carried out by the Virus Reference Laboratory, Colindale, London, were:

Specimen	*Day of illness*	*B1*	*B2*	*B3*	*B4*	*B5*
1	9	..	..	1/80	..	..
2	23	<1/10	<1/10	<1/80	<1/10	<1/10

Subsequent neutralisation tests over a period of three months showed titres of 1/64 for type B3. Routine laboratory investigations revealed no other significant features to account for the febrile illness: white blood-cells 9450 per c.mm.; anti-streptolysin titre positive 1/20 and negative 1/40; throat swab, *Streptococcus viridans*. The patient's convalescence was uneventful, and recovery was complete.

The neutralisation tests support the view that the patient had a Coxsackie-virus infection type B3. The acute febrile illness is typical of such an infection, especially the chest pains and pulmonary complications. Cardiac involvement in Coxsackie-virus infection is becoming more widely recognised, and this case of type-B3 infection adds to the ætiological factors of benign pericarditis.

EVAN FLETCHER
Belfast City Hospital. C. F. BRENNAN.

1. Reiss, M., Hemphill, R. E. *J. ment. Sci.* 1944, **90**, 681.
2. Fletcher, E., Brennan, C. F. *Lancet*, 1957, i, 913.

HOW TO BE HAPPY THOUGH RESIDENT

SIR,—Hospital administrators will read with lively appreciation the homily addressed to residents by Mr. Jennett, especially the reference to their relations with other departments of the hospital.

At this hospital, and doubtless in many others, an invitation is extended to the residents, upon taking up their posts, to meet the chief administrative officer in an endeavour to start off on the right foot, when assurance is given of the fullest cooperation by the administrative staff.

Although this is probably only practicable in medium-sized hospitals, experience shows that the simple gesture is usually appreciated.

Wembley Hospital. P. E. WINDO.

DISSEMINATION OF MICROORGANISMS BY A SURGICAL PUMP

SIR,—The article by Mr. Ranger and Dr. O'Grady (Aug. 9) revealed a possible, even likely, source of cross-infection in wards where mechanical suction is commonly used. Their remarks relate to the Middlesex type of machine, and they recommend an effective remedy.

This prompted a survey of all suction pumps in this group of hospitals, and the results of a few simple experiments show that we, at any rate, have been somewhat complacent.

The group possesses two diathermy machines with suction pumps, five of Guy's Hospital type, three of Middlesex type, and two of uncertain breed. The Middlesex machines are being dealt with as suggested by Mr. Ranger and Dr. O'Grady and are now safe. But the diathermy machines have no filter, and the exhaust is under the casing and discharges directly on to the floor. The Guy's type are fitted with filters consisting of two felt discs which are secured to the back of the machine by a metal case of which the outer half is secured by two small, grub-like screws which are awkward to remove and worse to replace.

The accompanying table shows the results of the admittedly primitive experiments.

It is evident that there is a potential danger from suction pumps, even when provided with a filter, if the filtering material is not replaced after use in a septic case. Ranger and O'Grady found that higher negative pressures produced more organisms at the outlet, but they refer to vacuums of 5–20 cm. Hg. The Guy's machine and the diathermy machines are designed to give up to 30 inches Hg! Possibly this is why surgeons seem to prefer them.

RESULTS OF BACTERIAL CULTURES

Source	Type of machine	Culture
Theatre I	*Guy's:* Inner disc	*Staph. albus*; *B. subtilis*; *Bact. aerogenes*; *Ps. pyocyanea*
	Outer disc	*Staph. albus*; non-hæmolytic streptococci; *Bact. aerogenes*; *B. subtilis*
Theatre II.. ..	*Guy's:* Inner disc	*B. subtilis*; paracolon bacillus; hæmolytic anaerobic streptococci (group G)
	Outer disc	*B. subtilis*; paracolon bacillus
Theatre III ..	*Guy's:* Inner disc	*Bact. alkaligenes*; *B. subtilis*
	Outer disc	*B. subtilis* only
Children's ward ..	*Guy's:* Both discs	Coagulase-negative *Staph. aureus* and an unidentified micrococcus
Neonatal ward ..	*Guy's:* Inner disc	*B. subtilis*
	Outer disc	Sterile
Theatre I* ..	*Diathermy*	*Ps. pyocyanea*
Theatre II* ..	*Diathermy*	*Staph. albus* overgrown by *B. subtilis*

* Obtained by holding a sterile celloidin membrane to the exhaust for three or four seconds.

Splashing always occurs in the container when the cavity being drained empties, or when the machine is switched off, and some organisms are bound to be drawn into the pump, and are ejected when it is next switched on. Contamination of the pump is naturally greater when suction is applied intermittently.

The remedy, in the case of the Guy's type of machine, is to replace the small screws by a spring clip, which permits changing of the filter discs without tears. The diathermy machines call for ingenuity in devising a trap which will not reduce the efficiency of the vacuum; probably enlarging the outlet hole, and leading a copper pipe to a trap attached to the machine, will meet most cases.

Victoria Hospital, Worksop, Notts. GAVIN DUNLOP.

FALSE GLYCOSURIA

SIR,—Bottles containing specimens of urine are brought to the general practitioner for testing. When one uses the newer preparations for rapid testing for glucose, mistakes may arise when the bottle contains contaminants.

Two specimens of urine brought to me in this way on successive days showed considerable glycosuria when tested by 'Testape' and 'Clinistix'; but both specimens failed to reduce Benedict's solution.

Both bottles had contained hydrogen peroxide, and, even though they had been washed before use, there was sufficient solution soaked in the screw cap to give a misleading result.

Although this must be an uncommon incident, the fact that hydrogen peroxide may mimic glycosuria in the rapid test should be borne in mind to save an occasional patient from unnecessary concern.

London, E.9. ALEC PHILLIPS.

DIAGNOSIS OF SICKLE-CELL ANÆMIA AFTER BLOOD-TRANSFUSION

SIR,—Severe anæmia is commonly seen in the children's department at University College Hospital, Ibadan. It is usually caused by malaria, malnutrition, or hookworm infestation or a combination of these, but it is quite often sickle-cell anæmia. From time to time a severely anæmic child is admitted and transfused before appropriate investigations have been undertaken to establish the diagnosis of sickle-cell anæmia. (The presence of the transfused normal erythrocytes in the patient's circulation interferes with interpretation of the hæmoglobin electrophoresis.) Under these circumstances it has been our practice to defer hæmoglobin electrophoresis, to establish the diagnosis of sickle-cell anæmia, until the transfused cells have disappeared from the circulation—usually a period of 3 to 4 months. The technique described below has recently been evolved in our departmental laboratory to obviate the time-lag in establishing the diagnosis.

The erythrocytes of normal individuals are usually completely lysed in 0·3% sodium chloride solution,[1] whereas in sickle-cell anæmia lysis usually only commences in 0·34% sodium chloride and is often complete only in 0·01% sodium chloride.[2] It is to be anticipated thus that lysis in 0·3% saline of blood obtained from a patient with sickle-cell anæmia after transfusion will result in destruction of all the normal cells,

1. Dacie, J. V. The Hæmolytic Anæmias. London, 1954.
2. Diggs, L. W., Bibb, J. *J. Amer. med. Ass.* 1939, **112**, 695.

leaving intact only cells containing sickle hæmoglobin. A hæmoglobin solution prepared from the remaining cells would be expected to show only the abnormal hæmoglobin. The

A B C

accompanying illustration shows the result of filter paper electrophoresis of different hæmoglobin solutions prepared from the blood of a patient with sickle-cell anæmia immediately after transfusion. Solution A was prepared by lysing all erythrocytes in distilled water. Solution B was prepared from cells which resisted lysis in 0·3% saline. Solution C is an A/S control. It will be seen that while A shows an A/S pattern, B shows hæmoglobin S only.

In sickle-cell/hæmoglobin-C disease and homozygous hæmoglobin-C disease the erythrocytes also show increased resistance to hypotonic saline solutions, and it is probable that these conditions could also be diagnosed with certainty in a recently transfused patient by employing this technique.

University College,
Ibadan, Nigeria. R. G. HENDRICKSE.

YOUTH CLUBS FOR THE HANDICAPPED

SIR,—Before retiring from the presidency of the Handicapped Children's Club, Bexleyheath, Kent, I should be grateful for the use of your columns to bring to notice the existence of this and similar organisations throughout the country.

The Bexleyheath club started in March, 1954, under the auspices of the local Society for Mentally Handicapped Children and was reorganised in September, 1955, as an independent Handicapped Children's Club in order to cater for children with any type of mental or physical handicap. At present there are 23 members (13 males and 10 females) and the majority are mentally defective. (The remainder include spastics, educationally subnormal, and maladjusted children.) The age range is 10 to 33 years with mental ages of approximately 3 to 9 years. Accommodation is provided in a local modern school and includes the use of a large hall, classrooms, garden, and playing-fields. Play materials are obtained by purchase from club funds and gifts from supporters; in addition, the school authorities have kindly granted the use of equipment. The regular staff consists of experienced and sympathetic voluntary workers, including 5 teachers from junior schools, 3 from occupation centres, and a few nursing and teaching students (the ratio of staff to members is roughly 1 to 3). Meetings take place fortnightly during the school term and are always well attended.

In April, 1956, an Independent Committee for Youth Clubs for the Handicapped was formed to promote the development of similar clubs in other areas. A ciné colour film, taken of the children's activities during the previous year, was shown in several districts of Kent and within 5 months a chain of clubs extended across North Kent. The success of this venture encouraged the committee to show the film in London and the South-Eastern Counties, and by January, 1958, 17 new clubs had opened. My latest information is that the campaign has spread to four other counties, 9 new clubs have been opened, and 17 districts are organising facilities.

I feel these clubs fulfil a useful function in the socialisation and education of handicapped children, and they afford the parents an opportunity to enjoy regular and frequent contact, thereby reducing their sense of isolation. The staff members, visiting speakers, and club library also help to dispel many misconceptions and old wives' tales concerning mentally handicapped children and thus alleviate much of the parents' self-blame and guilt. In addition, the club serves a more general function in the promotion of mental health by acting as a focal point of local interest in mental handicap, where individuals and organisations interested in this work may congregate, and where visitors from all sections of the public are welcome.

Further particulars regarding youth clubs for the handicapped may be obtained from Mr. J. B. Millwood, hon. secretary, 18, Martin Rise, Bexleyheath, Kent (telephone: Bexleyheath 7331).

Clatterbridge Hospital,
Bebington,
Cheshire. D. M. ZAUSMER.

THE TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

SIR,—Dr. Watson-Williams and his colleagues (Aug. 2) mention that they failed to find a recorded instance of a steroid-induced remission in a patient with a long history of purpura. A case I reported of an Indian boy who developed purpura in 1949 and had a temporary remission after splenectomy [1] may therefore be of more interest than I suspected.

In 1954 he was started on corticosteroid therapy and he has since been well controlled successively on cortisone, prednisone, prednisolone, and triamcinolone. He has now had a continuous remission of twenty-three months to date: this is certainly steroid-induced, for repeated attempts at reduction in his maintenance dosage of corticosteroids have resulted in prompt thrombocytopenia and bleeding gums. Of the corticosteroids used in this case, triamcinolone has had the greatest therapeutic potency and has also been the most effective.

General Hospital,
Singapore RONALD WELLS.

STORAGE OF INULIN IN RENAL TISSUE

SIR,—According to most authors inulin is the ideal substance for the determination of the glomerular filtration-rate. There is, however, in oliguric states a discrepancy between the clearances determined by the classical method and by the constant-infusion technique without collection of urine. Part of the infused inulin must thus be metabolised and/or excreted extrarenally and/or deposited in the organism. We have been interested in the storage of inulin in renal tissue.

Having re-examined the fact that, in spite of a constant plasma-inulin level, the excreted quantity is well below the infused one, we found that there is about 1·17–4·03 mg. of inulin per g. of kidney substance. This quantity, although significant, is too small to explain the difference between the infused and excreted amount during a clearance experiment of average duration.

In another experiment dogs made oliguric by hæmorrhage were given an infusion of inulin. The left kidney was then transplanted to the neck of a second dog, which was not given inulin. The urine of the transplanted kidney, as well as the recipient's urine, was collected until free of inulin, and the whole excreted quantity of inulin determined. The transplanted kidney was then analysed for the remaining inulin. The sum of the three quantities was in fair agreement with the inulin content of the right kidney removed at the same time as the transplantation of the left kidney.

The right kidney contained 1·03–5·75 mg. inulin per g.; the transplanted left one, having been "washed out" by the inulin-free blood and its own urine, contained only 0·22–1·84 mg. per g. (In 1 case we found 5·10 mg. per g.)

Our experiments seem to prove that some of the inulin infused can be stored in the kidney. Part of this quantity seems to be in the dead space of the urinary tract, part of it in the renal vessels and interstitium. There is, however, a small but significant quantity of inulin which remains stored in the renal tissue proper.

1. Wells, R. *Proc. Alumni Ass. Malaya*, 1957, **10**, 226.

Nevertheless, this seems to be too small to explain the diminished clearance values in oliguria, and an extrarenal disposition of inulin has to be supposed.

A detailed account of our data is to be published in *Acta physiologica hungarica*.

Physiological Institute, Medical University, Budapest.

P. BÁLINT
I. FORGÁCS.

"INCIDENCE" OF HYALINE MEMBRANE IN PREMATURE INFANTS

SIR,—We should like to call attention to a certain amount of confusion which exists with respect to estimates of the incidence of hyaline-membrane disease among premature infants. Since there is no infallible method of establishing this diagnosis during life, it has been the usual practice to determine the presence of this condition from the microscopic appearance of the lungs at necropsy. The incidence has then been computed as follows: (hyaline membrane/total necropsied infants) × 100 = % incidence. On the basis of these calculations those interested in this problem have been hard pressed to explain the high incidence of this condition among premature infants in the middle birthweight groups and the lower incidence among the lightest newborns.

We have examined our experience over a 7-year period (1950–57) in the premature nursery of the Babies' Hospital. During this interval 692 infants whose birthweight was less than 2001 g. were admitted to the premature nursery following birth in the Sloane Hospital for Women, the intramural obstetrical service of the Columbia-Presbyterian Medical Center. During the first three days of life 197 of these infants died. Necropsies were performed on 150, and 86 were found to have hyaline membrane in the lungs.

The "incidence" of this condition among these prematures is, of course, influenced markedly by the choice of a denominator population. Since we were interested in determining the influence of the degree of prematurity upon the incidence of this condition, and since the mean age at death is later for large than for small premature infants, we calculated rates specific for birthweight and age at death, and they appear in the accompanying table.

As can be seen the proportion of individuals examined at necropsy among those who died in the various age and birthweight categories was essentially the same. Therefore, we have reckoned the "incidence" to be the number of examples of hyaline membrane at necropsy among the total number of infants admitted (less those who died in the previous age interval). For the purpose of this calculation we have made the assumption that the mortality-rate associated with hyaline-membrane disease was the same in the three birthweight categories.

These estimates of the incidence of hyaline-membrane disease indicate that the condition occurs with equal or greater frequency among the lightest premature infants. If these approximations prove to be related to the true incidence of hyaline-membrane disease, we may have nothing to explain except the factor of prematurity itself.

We suggest, speculatively, that other conditions associated with an increased incidence of hyaline-membrane disease (e.g., maternal diabetes, cæsarean section, and placenta previa) may prove to be related only as the result of a common and unhappy association with prematurity.

Babies' Hospital, New York.

WILLIAM A. SILVERMAN
RUTH H. SILVERMAN.

GLOVES FOR NURSES

SIR,—The ineffectiveness of ordinary hand-washing is shown by the results of investigations on the bacteriology of the finger-tips of nurses.

In these investigations, which have been carried out regularly here for nearly three years, each nurse, straight from duty in the wards, presses the tips of the unwashed index, middle, and ring fingers of the right hand on the surface of half a sterile blood-agar plate. The nurse then washes her hands with toilet soap and hot water under a running tap, and dries both her hands on her individual sterile towel. The washed and dried index, middle, and ring fingers of her right hand are then again pressed on the surface of the second half of the sterile blood-agar plate. The blood-agar plate is incubated at 37°C for forty-eight hours and the colonies "before" and "after" are counted (1) after twenty-four hours' incubation, (2) after forty-eight hours' incubation, and the counts are recorded. The plates are then kept covered for some weeks on the bench at room-temperature and examined from time to time for late developers. Almost equal numbers of colonies develop in the "before" and "after" halves of the blood-agar plate.

In another series of experiments, the procedure was the same except that "after" the nurse dipped her dried fingers into strong commercial methylated spirit up to the proximal phalanx for exactly sixty seconds. The plate-counts "before" were unaltered, but the "after" counts were significantly altered—in fact, the "after" half of the plate was usually sterile. More than a hundred experiments on these lines were carried out, with results that varied only slightly.

We concluded that nurses should wear thin sterile rubber gloves when performing the following tasks: washing and shaving a patient before operation; washing a patient after death and preparing the body; routine washing of a patient; passing a catheter and obtaining a sterile specimen of urine; changing the napkins of a baby and cleaning its bottom; changing wound dressings; giving a patient a bedpan or urinal; cleaning the patient and taking the bedpan or urinal to the sluice, and handling these objects while washing and sterilising them, if these

"INCIDENCE" OF HYALINE MEMBRANE

Birthweight		⩽ 1000 grammes	1001–1500 grammes	1501–2000 grammes
	No. of infants admitted	116 infants	216 infants	360 infants
Died 0–23 hours	Died	56	33	20
	Necropsies	52	32	18
	Hyaline membrane	15	24	14
	% necropsied cases affected	(15/52) 29%	(24/32) 75%	(14/18) 78%
	"Incidence" in total population	(15/116) 13%	(24/216) 11%	(14/360) 4%
Died 24–47 hours	Died	22	21	21
	Necropsies	20	17	19
	Hyaline membrane	3	9	14
	% necropsied cases affected	(3/20) 15%	(9/17) 53%	(14/19) 74%
	"Incidence" in total population	(3/116–56) 5%	(9/216–33) 5%	(14/360–20) 4%
Died 48–71 hours	Died	9	8	7
	Necropsies	8	8	6
	Hyaline membrane	1	2	4
	% necropsied cases affected	(1/8) 13%	(2/8) 25%	(4/6) 67%
	"Incidence" in total population	(1/116–56–22) 3%	(2/216–33–21) 1%	(4/360–20–21) 1%

operations are done by hand; changing stained bed linen; counting dirty linen (better to count the linen after laundering); giving streptomycin injections and filling the syringe; handling sputum pots, sputum jars, fæcal-specimen jars or pots, and swab-tubes; giving enemas, taking rectal swabs, manipulating colostomy tubes, and handling empyema and other drainage tubes. Gloves also protect the skin of the nurse's hands from too frequent washing and drying.

In the interval between any two tasks, and while performing a lengthy task, the nurse dips her gloved hands into a dilute disinfectant such as dilute watery chlorinated lime, chlorhexidine, or even tricresol, and dries her gloved hands on a sterile towel.

In the absence of gloves, the conscientious nurse, following popular teaching, may find it necessary to wash and dry her hands more than a dozen times in a working day. This repeated washing and drying is bound to injure the epidermis and cause the hands to become rough and dry and cracked. This deterioration of the state of the skin is very serious; proper asepsis cannot be attained; and the nurse may develop a whitlow, which may incapacitate her for a week or more. When her lesion has healed, and she returns to work, the repeated washing and drying of her hands will start her troubles all over again. We are driven to the logical conclusion that the nurse should wear thin sterile rubber gloves, to prevent cross-infection and to protect her hands while at work.

St. Margaret's Hospital, Epping. Essex. FRANK MARSH.

RESERPINE IN SCHIZOPHRENIA

SIR,—Although reserpine ('Serpasil') has now been used widely in the treatment of schizophrenia it might be of interest briefly to record the results of this treatment in a small mixed group of patients during the period May, 1956, to May, 1957.

The 35 cases in this group consisted of insulin failures and relapses, or cases considered unsuitable for insulin therapy; thus, those with the best prognosis were excluded. Except that the patients were, in most cases, recent admissions, no other factors entered into their selection.

At the start of treatment, dosage varied from 8·5 mg. to 11·5 mg. daily for about six weeks. It was then gradually reduced, during the subsequent six to eight weeks, to 0·75 mg. daily. The duration of treatment varied from three or four months to a year, according to the duration of symptoms before treatment began and the willingness of the patient to cooperate after discharge from hospital. To minimise the risk of a suicidal depression, relatives were advised in writing to inform their doctor if the patient should become depressed and the doctor was advised to inform us. Most patients were discharged on trial for three to six months to give us further control of therapy. Definite depression, a rare occurrence, indicated cessation of treatment.

After discharge from hospital, patients received routine visits from the psychiatric social worker and were followed up at the outpatient clinic at two to four weekly intervals. While in hospital they had weekly interviews. Supervision continued for an average of six months to a year.

Patients were classified as "recovered" if they were fully socialised and revealed no overt psychotic manifestations, and as "relieved" if definite improvement rendered them capable of partial socialisation with marked diminution of psychotic symptoms. The results were as follows:

I: Simple.—2 cases of long duration. Failed.

II: Hebephrenic.—9 cases. 4 recovered (2 cases were of over two years' duration and 2 of short duration). 3 relieved, 1 since relapsed (all over two years' duration). 2 failed (1 over two years and 1 probably over two). 6 (67%) recovered and relieved in all (omitting relapse).

III: Paranoid.—19 cases. 9 recovered (4 over two years, 5 of short duration). 3 relieved (1 relapsed since, all over two years). 7 failed (all over two years). 11 (58%) recovered and relieved in all (omitting relapse).

IV: Catatonic.—3 cases. 1 recovered (short duration). 2 failed (over two years).

V: Puerperal.—2 of brief duration. 1 recovered, 1 relieved.

In I, IV, and V the numbers were too small to be significant. From such a small group no definite conclusions could be drawn, but we would record our clinical impressions:

(1) The cases most suitable for this form of therapy seem to be the colourless, apathetic type of hebephrenic. We also noted that the paranoid patients most helped revealed a flattened affect, lack of colour, and spontaneity. Patients with more colourful effect appeared to respond more satisfactorily to chlorpromazine.

(2) We feel it is important to continue serpasil in small doses, in cases of long duration, for upwards of a year, perhaps longer. This appears to lessen the likelihood of relapse. We had no case relapse while on maintenance treatment.

These comments are based on our hospital records up to June 30, 1958.

D. J. C. DAWSON
G. A. KERNOHAN
S. J. KNOX.

Londonderry and Gransha Hospital, Londonderry, Northern Ireland.

PRODUCTION OF LUNG CONSOLIDATION IN MICE BY STAPHYLOCOCCAL TOXINS

SIR,—Mice of mean body-weight 12 g., inoculated intranasally with a dose of from 0·1 to 1·2 mg. of *Staphylococcus aureus* (Terajima strain) under light anæsthesia did not die, and only a slight congestion of the lungs, without abscess formation, was observed. The inoculated organisms were gradually eliminated from the lungs within a few days. But each mouse inoculated intranasally with 0·05 ml. of a potent filtrate of the culture (prepared by the method described below) died with extensive hæmorrhagic consolidation of the lungs. There was intensive congestion, œdema, and hæmorrhage but no abscess formation. The filtrate plus the staphylococci produced extensive consolidation *with* abscess formation.

Staphylococci were cultured in a semisolid agar (pH 7·2) consisting of 2% peptone, 0·2% agar, 0·3% NaCl, 0·2% potassium phosphate, and 0·03% magnesium sulphate, in an atmosphere of 20% CO_2 at 37°C for 48 hours. The culture was centrifuged and the supernatant was filtered with Seitz EK to remove the organisms. The activity of the cell-free filtrate was titrated and the titre expressed as the highest dilution causing complete hæmolysis of rabbit erythrocytes in a 0·5% suspension after 1 hour's incubation at 37°C. Although the titre of the filtrate and the time till death of the inoculated mice was in an inverse relation, the limiting titre for cause of death was about 100.

The following experiments were made with a filtrate with a titre of 1600 as a consolidation-producing dose which brought about death within 14 hours. The power of producing consolidation and the hæmolytic activity of a filtrate were lost by heating at 60°C for 30 min., by treatment with formol (0·4%, 1 week incubation), or by treatment with a sufficient amount of rabbit red cells at 0°C (indicating the adsorption of the active substances to the red cells). An antiserum prepared by immunising a rabbit with formolised filtrate neutralised the consolidation-producing toxicity in vitro. These results suggest the presence of an intimate relation between alpha-hæmolysin [1] and consolidation-producing factor in the filtrate.

Each mouse was injected subcutaneously with a dose ranging from 100 to 500 μg. of tetraethylammonium bromide (T.E.A.), and 30 min. later a consolidation-producing dose of a filtrate was given intranasally. None of the mice died within 72 hours, and when killed they showed no consolidation. Each mouse of another group was injected subcutaneously with a dose ranging from 50 to 500 μg. of chlorpromazine, and 30 min. later a con-

1. Glenny, A. T., Stevens, M. F. *J. Path. Bact.* 1935, **40**, 201.

solidation-producing dose was given intranasally. As in the case of T.E.A. none of the mice died within 72 hours, and none showed pulmonary consolidation.

Penner and Klein [2] observed that direct contact of shiga neurotoxin and intestinal mucosa of dogs produced no lesion in the intestinal mucosa, whereas an intravenous injection of the toxin caused the appearance of a number of focal lesions, and that this phenomenon could be inhibited by injection of tetraethylammonium chloride.

We [3–5] have reported that each particle of influenza virus (PR8), Newcastle disease virus, or hæmagglutinating virus of Japan can cause, even when infectivity has been destroyed, pulmonary consolidation in the inoculated mice, and that the production of consolidation is completely prevented by a previous injection of an adequate dose of T.E.A. or chlorpromazine. Since these drugs interfere with the passage of autonomic impulses through the central nervous system, it appears that staphylococcal toxins, like shiga neurotoxin or some viruses, have their primary action on the nervous system itself.

Department of Bacteriology, School of Medicine, Nagoya University, Japan. KAZUO OGASAWARA SHOSEI TANAKA.

SINGLE DAILY DOSE OF CHLORPROMAZINE

SIR,—In my letter [6] last March, I described a trial of treatment of patients on a single *daily* maintenance dose of chlorpromazine, and mentioned that other wards than the "pilot" ward had since followed up this idea with success.

Further experience in these other wards shows that this success is only partial although the original pilot ward has carried on satisfactorily. Of a total of 70 female patients on chlorpromazine in two large chronic refractory wards, where this method has been tried, it has proved possible to maintain satisfactory results in 32 patients only (45%). There were no real problems during the first weeks after the change to daily dose, but gradually it became necessary to change and divide the dosage because some patients were unduly drowsy during the day, because some patients appeared pallid and listless or complained of vague malaise, and because, as is often the case on these wards, individual patients' pattern of illness required changes in medication.

I thought it necessary to make this further report, in that this experience serves strongly to reaffirm the necessity of constantly regulating dosage to the individual needs of patients.

All Saints Hospital, Birmingham. J. C. N. TIBBITS.

TEXTBOOKS: A NEW STYLE?

SIR,—The publication of a textbook in a cheap utility edition deserves your welcome (Aug. 30, p. 451), but it is no more than a hesitant step in the right direction. The cheap edition referred to costs about 60% of the standard edition—itself an abbreviated 220 pages. The suggestion that cheap textbooks could be obtained by limiting their contents does not solve the major problem. The need is not for more short textbooks, but for cheap paper-back editions of the large standard textbooks.

Few students can afford all the necessary textbooks at four or five guineas each. We are further deterred from buying by the rapidity with which new editions appear, causing medical value, and financial value on the second-hand market, to depreciate alarmingly fast.

It is clear that some subjects—for example, therapeutics—depending less on illustration are best suited to production on cheap paper. But the Pelican books on art and architecture show that both photographs and line drawings can be adequately represented in cheap paper-back volumes. Size should be no deterrent; if *War and Peace* can be published in two volumes for ten shillings, let a surgical textbook be published in three volumes for twice as much. If the publisher, following Continental custom, produces a really cheap edition with the pages still stuck together, no matter; here at last is a sure way for the student to find out what parts of the syllabus he has not covered.

Guy's Hospital, London, S.E.1. S. R. MEADOW.

THE GENERAL PRACTITIONER

SIR,—In his speech in the Lords' debate which you reported on July 12, Lord Moran spoke of a general decline in the status of the general practitioner.

It began, he said, "when people generally felt when they were seriously ill that they were well advised to go into hospital. That was extremely mortifying to the doctor. He found that the patient, in this particular crisis in his life, preferred to put himself into the hands of a complete stranger".[1]

Unfortunately I have not kept statistical records; but on looking through my files I find that, in my five-and-a-half years in general practice, 116 of my patients have been content to die under my care, as against 15 who have died in hospital (3 of whom were admitted as surgical emergencies and 2 had no choice, being certified and carried off willy-nilly). This leaves aside two or three who made no decision either way, and were taken care of by the coroner; but it scarcely bears out Lord Moran's contention, unless one assumes that people who prefer to die in their own beds do not regard themselves as seriously ill.

Admittedly many patients do go to hospital; but many return to their own doctor's care. The visiting-list of a general practitioner which you published on July 5 should give pause to anyone who supposes that the illnesses of general practice are trivial or that the family doctor finds himself without heavy medical responsibilities.

Kingston-on-Thames, Surrey. CHARLES STEER.

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

SIR,—Mr. Huckstep and Dr. Bodkin (Aug. 16) give an interesting account of the use of vagotomy to relieve painful hypertrophic pulmonary osteoarthropathy associated with bronchial carcinoma. I should like to record a case in which relief was given by a simpler method.

A man of 53 had bacteriologically proved pulmonary tuberculosis in 1955, for which segmental resection was performed. A hilar glandular mass appeared seven months later, and at thoracotomy an undifferentiated squamous-cell carcinoma was removed.

After another nine months he was readmitted with clubbing and fever, and painful œdema of hands and feet which had caused him to be bedridden for two weeks. (No finger clubbing had been present after the first operation.) As he appeared to have local recurrence of his growth, and hepatomegaly presumably due to metastasis, and as the condition of the extremities and fever were his only symptoms, he was started experimentally on a course of butazolidine, 200 mg. twice daily, on May 5, 1957. This was gradually reduced to 100 mg. daily. The fever and œdema of hands and feet disappeared dramatically, although some clubbing of fingers and toes remained. He was discharged home ambulant a month after starting the drug.

2. Penner, A., Klein, S. *J. exp. Med.* 1952, **96**, 59.
3. Ogasawara, K., Nakayama, M. *Virology* (in the press).
4. Ogasawara, K., Aida, M. *Virus, Kyoto*, 1958, **8**, 242.
5. Nakayama, M. *ibid.* p. 262.
6. *Lancet*, 1958, i, 689.

1. Parliamentary Debates (Hansard), House of Lords, July 2, 1958, col. 469.

Unfortunately he died at the end of 1957, but the painful œdema of the hands and feet did not recur while he was receiving butazolidine, which was continued for about four months in all.

In cases of this kind it may be worth trying butazolidine before embarking on vagotomy.

Colindale Hospital, London, N.W.9. DIANA OWEN.

HÆMOPHILIA-LIKE STATES IN GIRLS

SIR,—I read with great interest the article by Professor Quick and Miss Hussey in your issue of June 21, and I want to emphasise the following findings. We, too, observed, with the late Prof. E. Frank, 2 cases of deficiency of antihæmophilic globulin (A.H.G.) (thromboplastinogen) with prolonged bleeding-time.

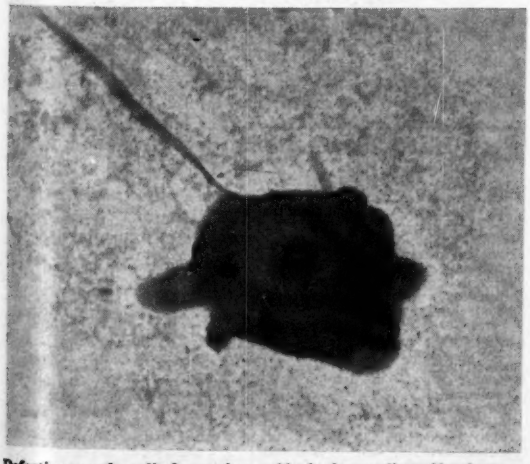
CASE 1.—A thirteen-year-old girl had an entirely negative family history. In childhood she had prolonged bleeding after minor cuts and bruised easily. She had severe epistaxis. The laboratory findings are summarised in the accompanying table.

Test	Case 1	Case 2	Normal
Bleeding-time (min.)	60	8–11	2
Coagulation-time (min.)	12–25	11	8
Prothrombin-time (Quick) (sec.) ..	12	12	12
Prothrombin-consumption time (Quick) (sec.)	10	15	34
Thromboplastin-generation test (Bigg-Douglas)	Abnormal	Abnormal	Normal
T.G.T. with normal $BaSO_4$-treated plasma (sec.)	8	9	...
Subject's $BaSO_4$-treated plasma substituted in the normal system ..	Abnormal	Abnormal	..
A.H.G. (%)	5	8	80–120

A.H.G.-deficiency was noted, and A.H.G. was 5%. The case was a pseudohæmophilia B (vascular hæmophilia or angiohæmophilia A). The cause of the prolonged bleeding-time was investigated and a platelet defect was observed under the electron microscope. The aggregation and adhesiveness, the formation of pseudopodia, and the spreading of hyalomere of platelets were absent or defective [1 2] (see fig.).

CASE 2.—A year later, a second similar case (an eleven-year-old boy) was observed and the platelet defect was noted under the electron microscope.[3]

1. Frank, E., Ulutin, O. N. *Bull. Soc. turq. Méd.* 1957, **23**, 301.
2. Frank, E., Ulutin, O. N., Pecikyan, R. (in the press).
3. Bilhan, N., Ulutin, O. N., Karaca, M., Sestakof, D. (in the press).



Defective pseudopodia formation and lack of spreading of hyalomere of platelet in a case of A.H.G.-deficiency with prolonged bleeding-time. (×15,000.)

These findings suggest that in vascular hæmophilia besides A.H.G.-deficiency there is a platelet defect as in the thrombasthenia described by Braunsteiner [4] and by ourselves.[5] In other words, these cases are combinations of thrombasthenia and hæmophilia (thrombasthenia hæmophilica). In these cases, the so-called Frank's athrombia [6 7] does exist—that is to say, the bleeding-time is prolonged because of defects in the aggregation and adhesiveness of platelets. The same defect of platelets has been observed by Paykoç and Erişilgil [8] in a case of Christmas disease with prolonged bleeding-time. This finding confirms our observations.

In my opinion, the third and fourth cases of Professor Quick are examples of the syndrome of thrombasthenia hæmophilica or athrombia hæmophilica.

Second Internal Clinic of Istanbul University, Guraba Hospital, Istanbul, Turkey. ORHAN NURI ULUTIN.

DIPLOMA OF CHILD HEALTH

SIR,—In your educational number (Aug. 30) you do not include the Royal Faculty of Physicians and Surgeons of Glasgow amongst those bodies which grant a diploma of child health. Reference to the advertisement pages of the same number will confirm that it does.

Royal Hospital for Sick Children, Glasgow, C.3. ROBERT A. SHANKS.

ACTION OF PSYCHOTROPIC DRUGS ON γ-AMINOBUTYRIC AND GLUTAMIC ACID IN RAT BRAIN

SIR,—Recently one of us (C. de W.) recorded [9] the results of an investigation into the inhibition of intermediary metabolism by some diphenhydramine derivatives. Like the barbiturates, diphenhydramine reduces the oxygen consumption during oxidation of glucose (rat-brain slices).[10]

Generally speaking, the alkyl-substituted derivatives have a similar but more pronounced effect. At the concentration used (0·002 M) the inhibition is antagonised by histamine. Another remarkable effect is seen in the action of these compounds on aminoacid metabolism. Paper chromatography showed that some of the compounds changed the level of at least two aminoacids which, to the best of our knowledge, were identified as glutamic acid and methionine. Of the compounds investigated orphenadrine (β-dimethylaminoethyl 2-methylbenzhydrylether, 'Disipal'), gave the strongest effect—an eleven-fold increase of glutamic acid and a more than seven-fold increase of "methionine". Orphenadrine, the pharmacological properties of which are quite different [11] from those of diphenhydramine, is used in the treatment of parkinsonism[12], but was recently found to have psychotropic activity[13]. These observations suggested that it might be useful to investigate the influence of psychotropic drugs on the aminoacid metabolism.

Using the "collidine" filter-paper technique of Dent [14] the influence of orphenadrine on the aminoacid spectrum was reinvestigated (substrate: glucose 0·02 M, orphenadrine 0·002 M, buffer medium pH 7·2, weight of brain slices 80–100 mg.). We were able to prove that the designation of one of the aminoacids mentioned above as "methionine" was incorrect, and that after the experiment γ-aminobutyric acid, as well as glutamic acid, was present in increased quantity.

4. Braunsteiner, H., Fellinger, K., Pakesch, F. *Klin. Wschr.* 1953, **31**, 21.
5. Alatas, S., Ulutin, O. N. *New Istan. contr. Clin. Sci.* 1954, **3**, 22.
6. Frank, E., Ulutin, O. N., Karaca, M. *ibid.* 1956, **4**, 62.
7. Frank, E. *Münch. med. Wschr.* 1958, **100**, 940.
8. Paykoç, Z., Erişilgil, O. (unpublished observation).
9. de Waart, C. Thesis, Vrije Universiteit, Amsterdam, 1958.
10. de Waart, C. *Acta physiol. pharmacol. Neerl.* 1956, **5**, 220; *ibid.* 1958 (in the press).
11. Bijlsma, U. G., Harms, A. F., Funcke, A. B. H., Tersteege, H. M., Nauta, W. T. *Arch. int. Pharmacodyn.* 1956, **106**, 332.
12. Gillhespy, R. O., Ratcliffe, A. H. *Brit. med. J.* 1955, ii, 352; Doshay, L. J., Constable, K. *J. Amer. med. Ass.* 1957, **163**, 1352.
13. Scheurle, G. *Dtsch. med. Wschr.* 1957, **82**, 2227.
14. Dent, C. E. *Biochem. J.* 1948, **43**, 169.

A preliminary investigation revealed that:

(*a*) Psychotropic drugs inhibit oxygen consumption of metabolising brain slices from 0 to 89% (molar concentrations as above).

(*b*) If they affect aminoacid metabolism γ-aminobutyric acid and glutamic acid are involved; in some cases only glutamic acid is present in larger concentration after the experiment.

The results so far are summarised in the accompanying table.

INHIBITION OF OXYGEN CONSUMPTION AND INCREASE IN AMINOACIDS

Drug (0·002 M)	% inhibition	Aminoacid increase factor (normal value = 1)	
	O^2 consumption	Glutamic acid	γ-aminobutyric acid
Chlorpromazine	89	7	10–20
Orphenadrine	59	7	10–20
Azacyclonol	36	4	1
Pipradrol	26	4	1
Benactyzine	25	3	1
Meprobamate	14	1	1
Adrenochrome (0·0005 M)	0	1	1
Deanol [15]	0	1	1

The inhibition of oxygen consumption by some psychotropic drugs is already known,[16] but it is not a specific property of these compounds. As far as we know their influence on the aminoacid metabolism has not been investigated.

During the past year γ-aminobutyric acid has attracted the attention of several investigators. Its occurrence as free acid in relatively large amounts in the brain and its pharmacological actions—e.g. on central synapses—are very interesting.[17]

We would not at the moment suggest that the action of some well-known psychotropic drugs could be explained by their influence on the γ-aminobutyric-acid and glutamic-acid level in the brain alone, but we think it useful to continue our investigations in this direction and into the possibility of a "biochemical classification" of psychotropic drugs.

We are indebted to Mr. W. F. Kafoe for his valuable help in the experiments.

Chemical Laboratory, Vrije Universiteit, Amsterdam. W. TH. NAUTA.
Laboratory for Chemical Physiology, Vrije Universiteit, Amsterdam. H. K. OOSTERHUIS
C. DE WAART.
Research Department, Brocades, Amsterdam. M. J. E. ERNSTING.

15. Pfeiffer, C. C., Jenney, E. H., Gallagher, W. *Science*, 1957, **126**, 610.
16. Bernsohn, J., Namajuska, I., Boshes, B. *J. Neurochem.* 1956, **1**, 145.
17. Purpura, D. P., Girado, M., Grundfest, H. *Science*, 1957, **125**, 1200; Marrazzi, A. S., Ross Hart, E., Rodriguez, J. M. *ibid.* 1958, **127**, 284; Roberts, E., Rothstein, M., Baxter, C. F. *Proc. Soc. exp. Biol., N.Y.* 1958, **97**, 796; Kuriaki, K., Yakushiji, T., Noro, T., Shimizu, T., Saji, S. *Nature; Lond.* 1958, **181**, 1336.

Public Health

Vaccination against Poliomyelitis

THE Minister of Health has issued details of the Government's plan for the extension of the poliomyelitis vaccination programme. This plan, based on the recommendations of the Joint Committee on Poliomyelitis Vaccine, with Lord Cohen of Birkenhead as chairman, falls broadly into three phases:

1. A drive to complete the vaccination of all those registered in the present priority groups and to raise the acceptance-rate among these groups as high as possible. The present groups are: (*a*) children aged 6 months to 15 years; (*b*) expectant mothers; (*c*) general practitioners, hospital staff in contact with poliomyelitis patients, ambulance staff, and the families of these groups.

2. Vaccination of those born in 1933–42, thus raising the upper age limit from 15 to 25.

3. Vaccination of a wider range of hospital staff—namely, all who come in contact with patients—and medical students and the families of these groups.

4. Third injections. It is suggested that these should be offered to all who have already had two, in approximately the same order in which they were given their earlier injections, and that an offer should be made as soon as possible to those who were vaccinated in 1956.

Fluoridation

THE considered opinion of an international group of experts is given in a report from the World Health Organisation on the value of fluoridation of public water-supplies for the prevention of dental caries.[1] This committee has no doubt about the efficacy, safety, or practicability of fluoridation: it draws attention to the mass of evidence that concentrations of 1 p.p.m. of fluorides, artificially or naturally present in drinking water, do no harm to health and go far to prevent decay of the teeth.

Unfortunately many members of the public do not see fluoridation in terms of compensating for a deficiency: they feel that something unnatural is being added, and they see possible danger to general health in drinking "doctored" water. The importance of such opposition was shown recently by the local decision to discontinue fluoridation of the water-supply at Andover—one of the places which were participating in the Ministry of Health's test of the method. At Andover, as in some towns in New Zealand, fluoridation had become an acute political issue, on which candidates in local elections were successful or defeated. As the result of a series of elections, the scheme ceased to command a majority on the council and the original decision to cooperate was reversed.[2]

The experience of New Zealand suggests that prejudiced opposition can be overcome by patient and vigorous instruction in the facts about fluoridation. In a programme of this kind, publicity should be given to experiences of local natural fluoridation of public water-supplies, such as that at Deeping St. James, in Kesteven, mentioned by the principal school medical officer for Lincolnshire in his annual report for 1957. In this area, the water has been naturally fluoridated at a constant level of 2·5 p.p.m. for no less than twenty years, and, to quote the report, "the markedly superior dental condition and oral hygiene of the children of Deeping St. James . . . provide striking evidence in favour of fluoridation of other water supplies."

If the public could be convinced that countless people in these islands have been drinking naturally fluoridated water all their lives, with no ill effects, and that there is no essential difference between natural and artificial fluoridation, the opposition to this valuable preventive measure would at least be greatly weakened.

1. Expert Committee on Water Fluoridation; 1st Report. World Health Organisation Technical Report Series no. 146. Geneva: W.H.O. 1958; pp. 25. Obtainable from H.M. Stationery Office (P.O. Box 569, London, S.E.1). 1*s.* 9*d.*

2. See *Lancet*, July 26, 1958, p. 204.

Infectious Diseases in England and Wales

Disease	Week ended August				
	2	9	16	23	30*
Diphtheria	4	3	2	2	—
Dysentery	536	368	338	384	376
Encephalitis:					
Infective	5	1	6	5	4
Post-infectious	6	2	3	4	1
Food-poisoning	261	173	287	226	397
Measles, excluding rubella	6307	5605	5102	3796	2810
Meningococcal infection	11	11	9	14	10
Ophthalmia neonatorum	32	21	16	36	21
Paratyphoid fever	9	5	5	4	4
Pneumonia, primary or influenzal	168	150	183	151	135
Poliomyelitis:					
Paralytic	37	51	57	42	46
Non-paralytic	28	22	29	35	32
Puerperal pyrexia	202	186	237	198	214
Scarlet fever	555	410	373	326	286
Smallpox	—	—	—	—	—
Tuberculosis:					
Respiratory	455	427	415	452	447
Meninges and C.N.S.	8	6	10	12	3
Other	55	68	65	69	62
Typhoid fever	1	4	4	4	6
Whooping-cough	710	608	713	770	810

*Not including late returns.

Obituary

RUPERT WATERHOUSE

M.D. Lond., F.R.C.P.

Dr. Rupert Waterhouse, for many years a leading Bath consultant with special interests in rheumatology and clinical pathology, died on Sept. 1 at the age of 85.

A Yorkshireman, he was born at Sheffield, the youngest son of John Hodgson Waterhouse, M.D. He was a descendant of Sir Gilbert Waterhouse, surgeon to Sheffield Royal Infirmary, and grandson of John Hodgson, who practised surgery in Birmingham. He was educated in Sheffield at the Collegiate School and at Wesley College, and studied medicine at St. Bartholomew's Hospital, qualifying in 1897. In 1901 he settled in Bath, where he ultimately became physician to the Royal United Hospital and the Royal National Hospital for Rheumatic Diseases; and, as his consultant practice spread, he was invited in turn to become visiting physician to the Victoria Hospital, Frome, and the cottage hospitals at Chippenham and Trowbridge. He was elected F.R.C.P. in 1929. He was a founder and past president of the Bath Clinical Society.

He served in the 1914-18 war first as a combatant in the North Somerset Yeomanry and later with the R.A.M.C. in Gallipoli, Egypt, Palestine, and France, and for two years he commanded the South West Mounted Brigade Field Ambulance before being gazetted to command the 4th Southern General Hospital. During the second world war he returned from retirement to take the place of the pathologist to the Royal United Hospital, who was on active service.

During his later years, immediately before he left active practice in 1945, he practised mainly as a consultant in clinical pathology. His description of the clinical entity of acute suprarenal insufficiency from bilateral adrenal hæmorrhage (*Lancet*, 1911, i, 577) is well known to clinicians as the Waterhouse-Friderichsen syndrome. Of his retirement L. H. writes:

"During his later years Waterhouse was much handicapped by deafness and by an increasing lameness associated with osteoarthritis and Paget's disease of the hip. In spite of these disabilities, he was never known to complain; he retained his dry sense of humour and often mordant wit until the end, and he will be remembered as one of the great physicians of Bath and perhaps the finest after-dinner speaker of his time in the West Country. He was always more interested in the art and science of medicine and in research than in building a large consultant practice. He stood for all that was honourable in the practice of medicine and was bitterly critical of any form of showmanship or self-advertisement. A great reader, he was also a very fine bridge-player and, despite his physical disabilities, continued to play until the end."

Dr. Waterhouse leaves a widow, a son, and a daughter.

Appointments

CUSACK, NORA, M.B. N.U.I., D.C.H., D.P.H.: senior assistant M.O. and school M.O., Castleford and Normanton, Yorkshire.

EVERED, L. J., M.R.C.S., D.M.R.D.: part-time consultant radiologist, Mansfield area hospitals, Nottinghamshire.

JACKSON, AGNES, M.B. Aberd.: assistant M.O.H., Ross and Cromarty.

LEVEAUX, V. M., M.B. Lond., M.R.C.P.: part-time consultant physician, Derby group of hospitals.

SANDLER, MERTON, M.B. Manc., M.R.C.P.: consultant chemical pathologist, Bernhard Baron memorial research laboratories, Queen Charlotte's Maternity Hospital, London.

Notes and News

PREVENTIVE MEDICINE IN ANCIENT PERU

THE Incas were an extraordinary people, and it is interesting to have the account of preventive and curative medicine among them which Sir Weldon Dalrymple-Champneys wrote after his visit to Peru and gave as his presidential address to the Royal Society of Medicine's historical section.[1] He points out that "though the curative side of the picture can be more or less matched in other cultures, the preventive side . . . was in many ways in advance not only of other contemporary civilizations, but of all throughout the world up to the end of the nineteenth century".

The Inca empire lasted from about A.D.1000 to the Spanish conquest.

The Inca State, Sir Weldon says, "was one of the most benevolent despotisms the world has ever seen, and certainly one of the most efficient. The State saw to it that every subject, whatever his age, ability or health, had sufficient housing, nourishment, clothing, and amusement . . . security in marriage, freedom of worship, protection from special industrial hazards, freedom from debt (there was no money), security from oppression (the Inca sovereigns never abused their power or allowed others to do so), and protection from enemies outside. All these benefits were theirs, provided that they were never idle during working periods, stayed in their own provinces except when going up to the capital, Cuzco, for a feast, and did not break the laws. The Incas, in fact, gave their subjects a moral code far in advance of the peoples surrounding them. . . ."

Though they had no written language, they had a method of recording statistics, and possibly certain simple facts.

"The instrument used to record such statistics was the famous *quipu* (or *quipo*), a cord from which hung numerous knotted strings of different colours, the position of the knots indicating units, tens, hundreds and thousands. Men were specially trained to make the quipus and to interpret them and they are believed to have recorded not merely statistics, but even historical events.

"A census of the whole population of the empire was carried out every year, the population being divided into age groups. The accuracy of these statistics was safeguarded by severe sanctions, for the keeper of the records (called the *quipu-camayu*) who did not know what he should know, or who lied, was punished with death, 'without hope of reprieve' and the Indian who ran away to escape the census was poisoned. Special envoys of the Inca called the people together for numbering, even when they were in *articulo mortis*.

"Though labour was compulsory, the sovereigns took care that it did not exceed the power of the individual, and for this purpose account was taken of age, sex, health and the nature of the work in question. Never were governors more careful of the health of their people." The mining of mercury, which gives rise to "tremors and nervous spasms", was forbidden, and so was fishing for pearls. Only a small number of Indians were sent to the coca plantations, situated in hot and unhealthy country, and these workers were always inhabitants of hot districts. For very laborious tasks there was a rota system.

"TEACH YOURSELF"

SINCE the Teach Yourself books were started some twenty years ago, about 300 have been issued, and their range of subjects is now astonishing. To celebrate the beginning of the 21st year there is now "A Concise Guide to Teach Yourself",[2] which in the words of Mr. Leonard Cutts, the editor, "is meant to introduce you, as agreeably as possible, to the infinite variety of knowledge, the endless things you could learn, and make, and do if life were only long enough".

In his foreword Mr. Ritchie Calder compares the series to the clandestine teaching movement, called "the Floating University", which flourished in Poland under the Czars. At any rate, he feels, the fact that the sale of these books runs into many millions suggests that "perhaps one is wrong in saying that we are becoming a nation of listeners-in and lookers-on". The authors include many whose names are widely respected; and Mr. Calder tells with relish the story of an undergraduate who scornfully rejected his advice to read one of the books—until he found that it was by his own professor.

1. *Proc. R. Soc. Med.* 1958, **51**, 385.
2. London: English Universities Press, 102, Newgate Street, E.C.1. 1958. Pp. 196. 2*s*.

SURVIVAL AFTER SHIPWRECK

In the world wars a high proportion of the deaths at sea were caused by drowning and exposure. Between shipwreck and rescue survivors need buoyancy and nutrition, and details of experimental studies and of the equipment and procedures adopted by the Admiralty can now be seen on film.

The Flotation Properties of Life-Jackets (16mm., silent, black-and-white, 12 minutes, Britain, 1945)[1] is a fascinating record of an investigation to discover whether a life-jacket lifted the head of an unconscious person out of the water. Prof. E. A. Pask, wearing a life-jacket, was anæsthetised by Sir Robert Macintosh and dropped repeatedly into a swimming-bath and a rough-water tank. The efficacy of the jacket is well shown in the film from both above and below water at normal speed and in slow-motion.

Survival at Sea (16mm., silent, black-and-white, 25 minutes, Britain, 1950–53)[2] shows a series of experiments conducted by the Department of Experimental Medicine, University of Cambridge, with various types of emergency rafts. Investigations included conditions encountered in moderate, arctic, and tropical climates.

Survival at Sea,[3] a recent film made by the Admiralty, shows in detail the equipment now used in the Royal Navy and the routine to be adopted by survivors. Part I: "Equipment" (16 and 35 mm., sound, black-and-white, 20 minutes, Britain, 1956) begins with a demonstration of the inflation and maintenance of a life-jacket, and then the inflatable life-raft and its associated survival-pack are described in detail. The second half of the film is devoted to an exercise in which a raft is inflated and boarded. The importance of maintaining body-fluid is emphasised, and accordingly fresh water and a plentiful supply of anti-seasickness tablets are provided. Facilities for collecting rain water and a "solar still" are supplied. Part II: "Living on Air" (16 and 35 mm., sound, black-and-white, 32 minutes, Britain, 1957) is a dramatised account of life in a raft pending rescue. Duties are allocated, and an inventory check showing the position of all the items in the raft and in the survival pack is carried out. Boredom is relieved by a pack of cards and a comprehensive instruction book detailing the routine duties—times for issuing rations and so on. Each man is given one pint of water daily to be drunk in the evening, next morning, and the remainder at midday. Sufficient water for five days is provided, and as none should be consumed on the first day the survivors should be in good condition for six days. Glucose sweets complete the rations. The photography, all in sunny Mediterranean weather, is excellent.

Royal Faculty of Physicians and Surgeons, Glasgow

On Aug. 29 Prof. Stanley Alstead, the president, conferred honorary fellowships on Sir Alexander Fleck, Sir Maurice Bloch, Prof. Carl Browning, and Mrs. Stirling of Keir.

On Sept. 1 the following were admitted to the fellowship:

Sukumar Mukherjee, Raojabhai Ranchodbhai Patel, T. F. Rodger, George Rutledge, Thomas Symington.

British Institute of Radiology

This institute will hold a meeting at 32, Welbeck Street, London, W.1, on Friday, Oct. 17, when short papers on work in progress in radiobiology will be read.

Committee on Artificial Insemination

The Government have now announced the names of the committee which, under the chairmanship of Lord Feversham, is to inquire into the practice of human artificial insemination and its legal consequences. The members are:

Dr. L. Priscilla FitzGibbon, anæsthetist to a group of Gloucestershire hospitals and a juvenile court magistrate; Mrs. Peggy Jay, wife of Mr. Douglas Jay, M.P. for Battersea North, and a member of London County Council; Dr. D. T. McDonald, a general practitioner, Belford, Northumberland; Mr. Ralph Risk, president of the Law Society of Scotland, 1957–58; Mr. John Ross, formerly head of the Children's Department, Home Office, and chairman of the Marriage Guidance Training Board; Mr. Justice Stevenson, Q.C., a High Court judge; Dr. R. E. Tunbridge, professor of medicine, University of Leeds; and Mrs. H. Whitley, wife of the minister of St. Giles' Catherdral, Edinburgh.

The secretary of the committee is Mr. R. F. D. Shuffrey, Home Office, Whitehall, London, S.W.1.

1. Available from Sir Robert Macintosh, F.R.A.R.C.S., Radcliffe Infirmary, Oxford.
2. Available on hire from the British Film Institute, 4, Great Russell Street, London, W.1.
3. Available on hire or sale from the Director of Stores (10c), Admiralty, Whitehall, London, S.W.1. (Catalogue no. A635.)

University College, Ibadan

Mr. W. W. Davey has been appointed to the chair of surgery.

Mr. Davey graduated M.B. from Queen's University, Belfast, in 1935, and after holding demonstratorships there in physiology and anatomy took the F.R.C.S.I. in 1941. For the next five years he served with the R.A.F. Medical Service, and he landed in Normandy on D-day with a surgical team. In 1946 he was appointed chief surgical assistant to the gastroenterological unit at St. James's Hospital, Balham. In 1949 he took the F.R.C.S., and the following year he took up his present consultant appointment as gastroenterological surgeon to Whittington Hospital and New End Hospital, London. He gave a Hunterian lecture at the Royal College of Surgeons of England last year, and his published work includes papers on partial gastrectomy for peptic ulcer in the aged and on Rovsing's sign.

Dr. G. M. Edington has been appointed to the chair of pathology.

Dr. Edington graduated M.B. from the University of Glasgow in 1935, and after holding a resident appointment at Stobhill Hospital he joined the R.A.M.C. and served in India and Burma. He was demobilised with the rank of major in 1946 and soon afterwards joined the Colonial Service. He served at first as a pathologist in the Gold Coast (now Ghana), and in 1947 he took the D.T.M.H. In 1951 he took the D.C.P., and in 1953 he obtained his M.D. with high commendation. The following year he was appointed specialist pathologist in charge of the medical research institute and laboratory services of the Gold Coast. In 1957 he returned to this country to take up his present post of consultant pathologist to Whiston and Rainhill Hospitals in the Liverpool region. This year he was appointed M.B.E. in recognition of his services in Ghana. His published work includes papers on sickling and on abnormal hæmoglobin diseases.

The Privy Council has recognised the clinical facilities at University College Hospital, Ibadan, for the purpose of the degrees of M.B., B.S., of the University of London for an initial period of three years.

St. Luke's Day Service

A service for doctors is to be held at All Souls' Church, Langham Place, London, W.1, at 11 A.M. on Sunday, Oct. 19. Lord Moran and Sir Cecil Wakeley will read the lessons.

Seats will be reserved for doctors and their families. Application (stating the number of tickets required) should be made to the church secretary at All Souls' Church by Oct. 16.

Institute of Directors

This institute has set up a medical research unit to inquire into the health problems of directors. The director in charge of the unit is Dr. H. Beric Wright, F.R.C.S., formerly on the staff of the Shell Group.

On Friday, Oct. 3, at 3 P.M., Prof. Dorothy Russell will give the inaugural address to the Royal Free Hospital School of Medicine, Hunter Street, London, W.C.1.

On Monday, Oct. 6, at 3 P.M., Sir Christopher Hinton will give the inaugural address to the Westminster Medical School at Church House, Great Smith Street, London, S.W.1.

A conference of surgeons of the St. John Ambulance Brigade will be held at the B.M.A. House, London, W.C.1, on Nov. 1 and 2.

Group-Captain H. P. R. Smith has been appointed president of the central medical board and adviser in aviation physiology at the central medical establishment of the Royal Air Force.

The Friends of Blandford Hospital have opened a fund to provide a memorial to the late Dr. W. H. C. Spooner at the hospital. Donations should be sent to the treasurer, 6, West Street, Blandford.

The Hand Club of Great Britain and the Second Hand Club are meeting at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, on Saturday, Nov. 22, from 10 A.M. Further particulars may be had from Mr. H. Graham Stack, hon. secretary of the Second Hand Club, at 150, Harley Street, W.1.

The annual dinner of the Sheffield Medical School Old Students' Association will be held in the Firth Hall of the university on Saturday, Oct. 11, at 7 P.M. Further particulars may be had from Dr. J. D. H. Linfoot, department of pathology, Western Bank, Sheffield, 10.